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(21) International Application Number: PCT/US96/11022 (22) International Filing Date: 26 June 1996 (26.06.96) (30) Priority Data: 60/002.251 29 June 1995 (29.06.95) US 9603091.1 14 February 1996 (14.02.96) GB (71) Applicants (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). BANYU PHARMACEUTICAL CO., LTD. [JP/JP]; 2-3, Nihombashi, Honcho 2-chome, Chuo-ku, Tokyo 103 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): CASKEY, Charles, T. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). NISHIMURA, Susumu [JP/JP]; 2-3, Nihombashi, Honcho 2-chome, Chuo-ku, Tokyo 103 (JP). YONEMOTO, Mari [JP/JP]; 2-3, Nihombashi, Honcho 2-chome, Chuo-ku, Tokyo 103 (JP). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COMBINATIONS OF INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE (57) Abstract <p>The present invention relates to compositions comprising amounts of at least two therapeutic agents selected from a group consisting of a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to the protein substrate of the enzyme and a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to farnesyl pyrophosphate. Further contained in this invention are methods of inhibiting farnesyl-protein transferase and treating cancer in a mammal, which methods comprise administering to said mammal, either sequentially in any order or simultaneously, amounts of at least two therapeutic agents selected from a group consisting of a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is a competitive inhibitor with respect to the protein substrate of the enzyme and a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is a competitive inhibitor with respect to farnesyl pyrophosphate, in amounts sufficient to achieve an additive or synergistic therapeutic effect. The invention also relates to methods of preparing such compositions.</p>		

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TITLE OF THE INVENTIONCOMBINATIONS OF INHIBITORS OF FARNESYL-PROTEIN
TRANSFERASE5 RELATED APPLICATION

The present patent application is based upon copending provisional application Serial No. 60/002,251, filed June 29, 1995, priority of which is claimed hereunder.

10 BACKGROUND OF THE INVENTION

The Ras protein is part of a signaling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem.* 62:851-891 (1993)). Mutated *ras* genes are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

25 Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa¹-Aaa²-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al.*, *Nature* 310:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a

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C₁₅ or C₂₀ isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem.* 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics* 30:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational farnesylation. Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem.* 269, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993) and G.L. James *et al.*, *Science*, 260:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci U.S.A.*, 91:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science* 245:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al.*, *Cell*, 62:81-88 (1990); Schaber *et al.*, *J. Biol. Chem.*, 265:14701-14704 (1990); Schafer *et al.*, *Science*, 249:1133-1139 (1990); Manne *et al.*, *Proc. Natl. Acad. Sci USA*, 87:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in

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cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

5 Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are competitive with farnesyl diphosphate (FPP) and can be structural analogs of FPP or not directly analogous. The second class of inhibitors are competitive with the protein substrates (e.g., Ras) for the enzyme. The protein substrate-competitive inhibitors that have been described are generally cysteine
10 containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et. al.*, *ibid*; Reiss *et al.*, *PNAS*, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein
15 transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993); Graham, *et al.*, *J. Med. Chem.*, 37, 725 (1994)). Recently, protein substrate-competitive inhibitors that lack a thiol moiety have been described (WO 95/09000; WO 95/09001; WO 95/10514; WO 95/10515;
20 WO 95/10516; WO 95/08542; WO 95/11917; and WO 95/12612).

 Inhibitors of FPTase have recently been described that incorporate characteristics of both farnesyl pyrophosphate and the CAAX motif (R.S. Bhide *et al.*, *Bioorg. Med. Chem. Lett.*, 4:2107-2112 (1994) and (V. Manne *et al.*, *Oncogene*, 10:1763-1779 (1995)). Such a
25 bisubstrate strategy addresses the unfavorable entropic effect that might exist in bringing two molecules together at the same enzyme protein. However, the spatial requirements for accessing two enzymatic site interactions with a single compound may result in a bisubstrate inhibitor with a molecular weight and correspondingly poor pharmacokinetic
30 properties. Furthermore, the reported bisubstrate analogs have shown limited activity in cell-based assays.

 It is, therefore, an object of this invention to develop pharmaceutical compositions which comprise two different independent farnesyl protein transferase inhibitors, one inhibitor which is a

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competitive inhibitor with respect to the protein substrate of FPTase and the other inhibitor which is a competitive inhibitor with respect to farnesyl pyrophosphate. It is a further object of this invention to develop methods of inhibiting farnesyl protein transferase and treating cancer
5 utilizing these chemotherapeutic compositions.

SUMMARY OF THE INVENTION

The present invention relates to compositions comprising amounts of at least two therapeutic agents selected from a group
10 consisting of a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to the protein substrate of the enzyme (also referred to as a protein substrate-competitive inhibitor) and a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect
15 to farnesyl pyrophosphate (also referred to as a farnesyl pyrophosphate-competitive inhibitor) . Further contained in this invention are methods of inhibiting farnesyl-protein transferase and treating cancer in a mammal, which methods comprise administering to said mammal, either sequentially in any order or simultaneously, amounts of at least two
20 therapeutic agents selected from a group consisting of a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is a competitive inhibitor with respect to the protein substrate of the enzyme and a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is a competitive inhibitor with respect
25 to farnesyl pyrophosphate, in amounts sufficient to achieve an additive or synergistic therapeutic effect. The additive or synergistic therapeutic effect of the instant compositions may be achieved with smaller amounts of either or both of the protein substrate-competitive inhibitor and farnesyl pyrophosphate-competitive inhibitor than would be required if
30 such a protein substrate-competitive inhibitor or farnesyl pyrophosphate-competitive inhibitor were administered alone, thereby avoiding any non-mechanism-based adverse toxicity effects which might result from administration of an amount of the single protein substrate-competitive

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inhibitor or farnesyl pyrophosphate-competitive inhibitor sufficient to achieve the same therapeutic effect.

BRIEF DESCRIPTION OF THE FIGURES

5

FIGURES 1A, 1B and 1C: *In vivo Assessment of a Combination of Compound D and Compound E:*

Figure 1A shows the partial densitometric scan of an autoradiograph of a Western blot from the SDS-PAGE gel of the method described in
10 Example 21 wherein the FPTase inhibitory compound was Compound D at a concentration of 30 μ M. Figure 1B shows the partial densitometric scan of an autoradiograph of a Western blot from the SDS-PAGE gel of the method described in Example 21 wherein the FPTase inhibitory compound was Compound E at a concentration of 0.3 μ M. Figure 1C
15 shows the partial densitometric scan of an autoradiograph of a Western blot from the SDS-PAGE gel of the method described in Example 21 wherein a combination of FPTase inhibitory compounds was utilized (Compound D at a concentration of 30 μ M and Compound E at a concentration of 0.3 μ M).

20

FIGURE 2A and 2B: *In vivo Assessment of a Combination of Compound C and Compound A:*

Figure 2A graphically illustrates the data from a Western blot from the SDS-PAGE gel of the method described in Example 21 wherein the
25 FPTase inhibitory compound was Compound C at various concentrations. Figure 2B graphically illustrates the data from a Western blot from the SDS-PAGE gel of the method described in Example 21 wherein a combination of FPTase inhibitory compounds (Compound C at various concentrations and Compound A at a concentration of 0.03 μ M) was
30 utilized.

DETAILED DESCRIPTION OF THE INVENTION

The term "synergistic" as used herein means that the effect achieved with the methods and compositions of this invention is greater
35 than the sum of the effects that result from methods and compositions

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comprising the farnesyl-protein transferase inhibitors of this invention separately and in the amounts employed in the methods and compositions hereof.

5 The term "additive" as used herein means that the effect achieved with the methods and compositions of this invention is equal to the sum of the effects that result from methods and compositions comprising the farnesyl-protein transferase inhibitors of this invention separately and in the amounts employed in the methods and compositions hereof.

10 According to one aspect of this invention, it is now possible to achieve an additive or synergistic therapeutic effect in a mammal with amounts of a protein substrate-competitive inhibitor and farnesyl pyrophosphate-competitive inhibitor which, if administered in said amounts singly, are not capable of achieving said effect. The preferred
15 therapeutic effects achieved according to this aspect of the invention are inhibition of farnesyl-protein transferase in a mammal in need of such inhibition and treatment of cancer. The administration of the protein substrate-competitive inhibitor and farnesyl pyrophosphate-competitive inhibitor can be sequential in time or simultaneous with the simultaneous
20 method being preferred.

Because of the additive or synergistic therapeutic effects achieved by administration of a protein substrate-competitive inhibitor and a farnesyl pyrophosphate-competitive inhibitor, this invention provides particularly advantageous methods of achieving a therapeutic
25 inhibition of farnesyl-protein transferase and treatment of cancer with less than therapeutic levels of a protein substrate-competitive inhibitor and/or a farnesyl pyrophosphate-competitive inhibitor. Therefore, in practicing this invention, it is possible to minimize potential adverse effects which are not associated with inhibition of farnesyl-protein transferase and may
30 be associated with larger, therapeutic doses of the protein substrate-competitive inhibitor and/or the farnesyl pyrophosphate-competitive inhibitor, and still achieve a farnesyl-protein transferase inhibiting or cancer treating effect.

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The present invention is not limited in any way by the specific protein substrate-competitive inhibitor and/or farnesyl pyrophosphate-competitive inhibitor but is applicable to such protein substrate-competitive inhibitors and farnesyl pyrophosphate-competitive inhibitors now known or subsequently discovered or developed. Farnesyl-protein transferase inhibitors useful in the instant invention are described hereinbelow. It is the co-administration of a protein substrate-competitive inhibitor and a farnesyl pyrophosphate-competitive inhibitor as taught by this invention and not the particular protein substrate-competitive inhibitor and/or farnesyl pyrophosphate-competitive inhibitor which brings about the additive or synergistic effect of this invention. Nonetheless, the preferred protein substrate-competitive inhibitors for use in the methods and compositions of this invention and preferred farnesyl pyrophosphate-competitive inhibitors are described hereinbelow.

The composition of the instant invention may comprise a protein substrate-competitive inhibitor that incorporates a cysteinyl or sulfhydryl containing moiety at the N-terminus of the molecule. Thus the following compounds, well known in the art, are useful as protein substrate-competitive inhibitors in the instant invention:

- a) a peptide that comprises the amino acids CA₁A₂X, wherein:
- C = cysteine;
 - A₁ = an aliphatic amino acid;
 - A₂ = an aliphatic amino acid; and
 - X = any amino acid;
- b) Cys - Xaa¹ - Xaa² - Xaa³ - NRR¹, wherein
- Cys = cysteine;
 - Xaa¹ = any amino acid in the natural L-isomer form;
 - Xaa² = any amino acid in the natural L-isomer form; and
 - Xaa³ - NRR¹ = an amide of any amino acid in the natural L-isomer form, wherein R and R¹ are independently selected from hydrogen, C₁-C₁₂ alkyl, aralkyl, or unsubstituted or substituted aryl;

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c) Cys - Xaa¹ - Xaa² - Xaa³, wherein

Cys = cysteine;

Xaa¹ = any amino acid;

5 Xaa² = the amino acid phenyl alanine or a p-fluorophenylalanine; and

Xaa³ = any amino acid;

d) Cys - Xaa¹ - dXaa² - Xaa³, wherein

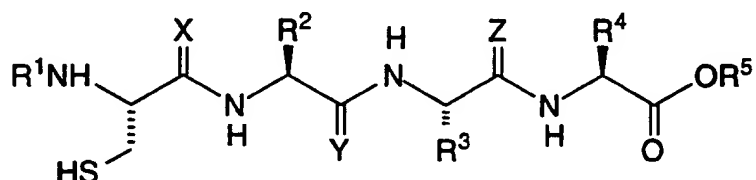
10 Cys = cysteine;

Xaa¹ = any amino acid in the natural L-isomer form;

dXaa² = any amino acid in the natural L-isomer form; and

Xaa³ = any amino acid in the natural L-isomer form;

15 e) U.S. Pat. No. 5,238,922, incorporated herein by reference,



wherein:

X, Y, and Z are independently H₂ or O, provided that at least one of these is H₂;

20

R¹ is H, an alkyl group, an acyl group, an alkylsulfonyl group or aryl sulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms, or in the alternative, R¹NH may be absent;

25

R², R³ and R⁴ are the side chains of naturally occurring amino acids, or in the alternative may be substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl or

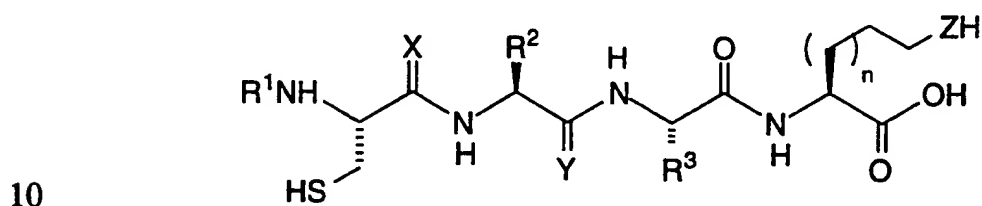
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saturated chains of 2 to 8 carbon atoms, wherein the aliphatic substituents may be substituted with an aromatic or heteroaromatic ring; and

- 5 R^5 is H or a straight or branched chain aliphatic group, which may be substituted with an aromatic or heteroaromatic group;

f) U.S. Pat. No. 5,340,828, incorporated herein by reference,



wherein:

X and Y are independently H₂ or O, provided that at least one of these is H₂;

- 15 R^1 is H, an alkyl group, an acyl group, an alkylsulfonyl group or aryl sulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms, or in the alternative, R^1NH may be absent;

20

R^2 and R^3 are the side chains of naturally occurring amino acids, or in the alternative may be substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl or saturated chains of 2 to 8 carbon atoms, wherein the aliphatic substituents may be substituted with an aromatic or heteroaromatic ring;

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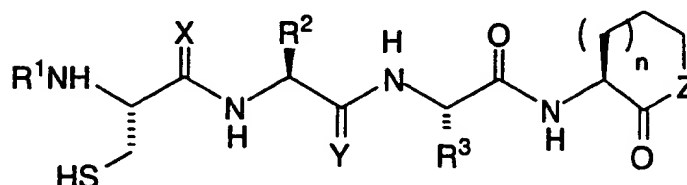
Z is O or S; and

30

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n is 0, 1 or 2;

g) U.S. Pat. No. 5,340,828, incorporated herein by reference,



5 wherein:

X and Y are independently H₂ or O, provided that at least one of these is H₂;

10 R¹ is H, an alkyl group, an acyl group, an alkylsulfonyl group or aryl sulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms, or in the alternative, R¹NH may be absent;

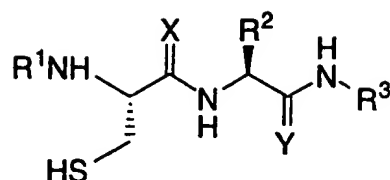
15 R² and R³ are the side chains of naturally occurring amino acids, or in the alternative may be substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl or saturated chains of 2 to 8 carbon atoms, wherein the aliphatic substituents
20 may be substituted with an aromatic or heteroaromatic ring;

Z is O or S; and

25 n is 0, 1 or 2;

h) U.S. Pat. No. 5,352,705, incorporated herein by reference,

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wherein:

X and Y are independently H₂ or O;

5

R¹ is an alkyl group, hydrogen, an acyl group, an alkylsulfonyl group or arylsulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbons atoms, which alternatively may be substituted with an aryl group;

10

R² is the side chains of naturally occurring amino acids, or in the alternative may be substituted or unsubstituted aliphatic, aromatic or heterocyclic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl or saturated chains of 2 to 8 carbon atoms which may be branched or unbranched, wherein the aliphatic substituents may be substituted with an aromatic or heteroaromatic ring;

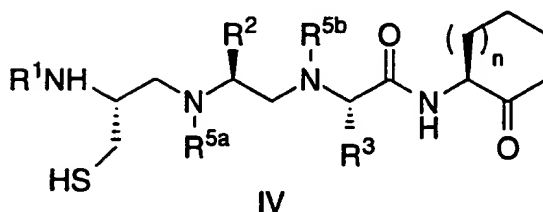
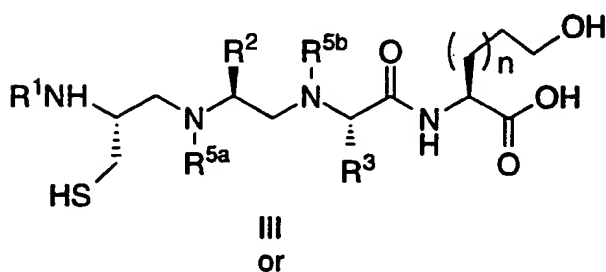
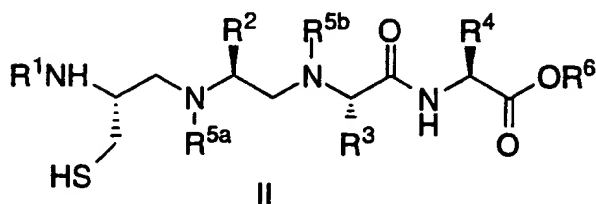
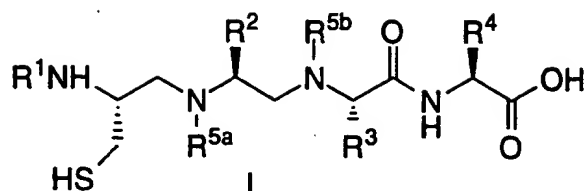
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R³ is an aromatic or heteroaromatic ring or in the alternative an alkyl group or an aryl or heteroaryl substituted alkane, wherein the aromatic ring is unsubstituted or in the alternative, substituted with one or more groups which may be alkyl, halo, alkoxy, trifluoromethyl, or sulfamoyl groups, and which may be polycyclic;

25

i) U.S. Pat. No. 5,326,773; PCT Publication WO 94/10137 and U.S. Serial No. 08/346,701, incorporated herein by reference,

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wherein:

5

R^1 and R^{5a} are independently selected from:

hydrogen, a C1-C6 alkyl group, a C1-C6 acyl group, an aryl group, a C1-C6 alkylsulfonyl group, C1-C6 aralkylsulfonyl group or arylsulfonyl group

10

wherein the alkyl group and acyl group is optionally substituted with substituted or unsubstituted aryl or heterocycle;

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R², R³ and R⁴ are independently selected from:

- 5 a) a side chain of naturally occurring amino acids,
 b) an oxidized form of a side chain of naturally occurring
 amino acids selected from methionine sulfoxide and
 methionine sulfone,
 c) substituted or unsubstituted C₁-C₈ alkyl, C₃-C₈
 cycloalkyl, C₂-C₈ alkenyl, aryl or heterocycle groups,
 wherein the aliphatic substituent is optionally substituted
10 with an aryl, heterocycle or C₃-C₈ cycloalkyl;

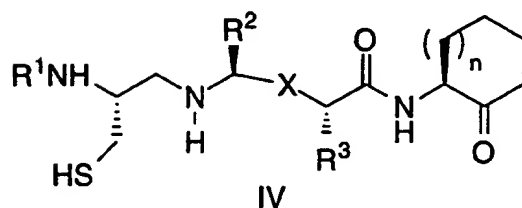
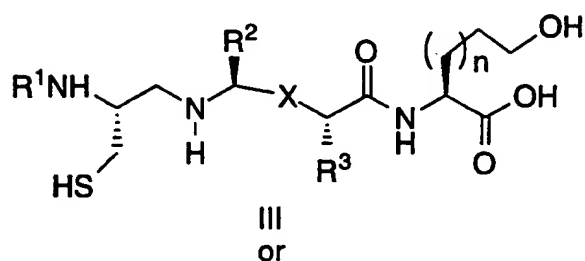
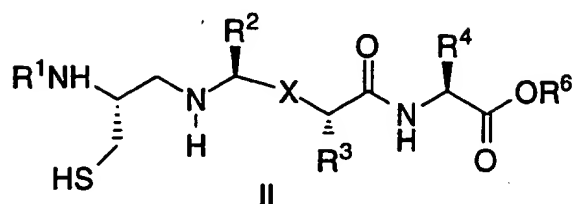
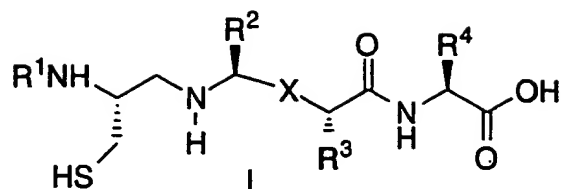
 R^{5b} is a C₁-C₆ alkyl group, a C₁-C₆ acyl group, an aroyl group, a
 C₁-C₆ alkylsulfonyl group, C₁-C₆ aralkylsulfonyl group or
 arylsulfonyl group
15 wherein the alkyl group and acyl group is optionally
 substituted with substituted or unsubstituted aryl or
 heterocycle;

 R⁶ is a substituted or unsubstituted aliphatic, aryl or heterocyclic
20 group, wherein the aliphatic substituent is optionally
 substituted with an aryl or heterocyclic ring; and

 n is 0, 1 or 2;

25 j) U.S. Pat. No. 5,504,212, incorporated herein by reference,

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wherein:

5

R¹ is selected from:

hydrogen, a C₁-C₆ alkyl group, a C₁-C₆ acyl group, an
 aroyl group, a C₁-C₆ alkylsulfonyl group, C₁-C₆
 aralkylsulfonyl group or arylsulfonyl group

10

wherein the alkyl group and acyl group is optionally
 substituted with substituted or unsubstituted aryl or
 heterocycle;

- 15 -

R^2 , R^3 and R^4 are independently selected from:

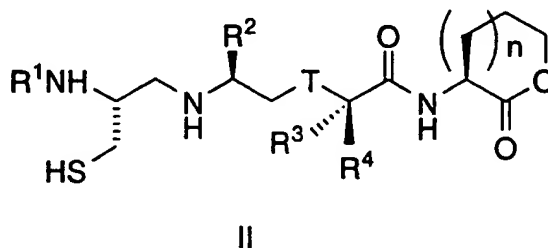
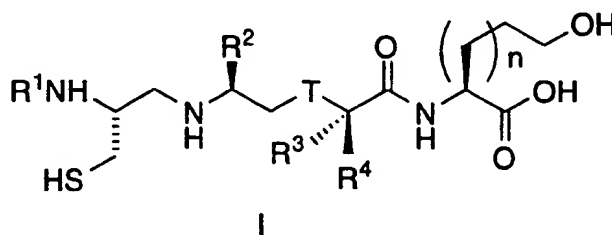
- a) a side chain of naturally occurring amino acids,
- b) an oxidized form of a side chain of naturally occurring amino acids selected from methionine sulfoxide and methionine sulfone,
- c) substituted or unsubstituted C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₂-C₈ alkenyl, aryl or heterocycle groups, wherein the aliphatic substituent is optionally substituted with an aryl, heterocycle or C₃-C₈ cycloalkyl;

X is CH_2CH_2 or trans $\text{CH}=\text{CH}$;

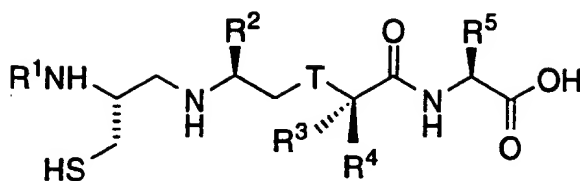
R^6 is a substituted or unsubstituted aliphatic, aryl or heterocyclic group, wherein the aliphatic substituent is optionally substituted with an aryl or heterocyclic ring; and

n is 0, 1 or 2;

k) PCT Publication WO 94/10138 and U.S. Serial No. 08/143,943, incorporated herein by reference,

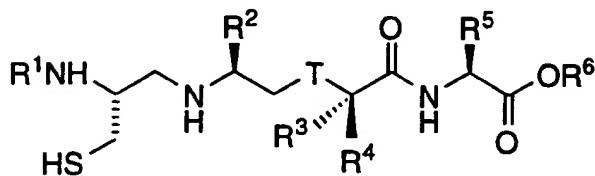


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III

or



IV

wherein,

5 R¹ is hydrogen, an alkyl group, an aralkyl group, an acyl group, an aracyl group, an aroyl group, an alkylsulfonyl group, aralkylsulfonyl group or arylsulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms;

10

R², R³ and R⁵ are

15

the side chains of naturally occurring amino acids, including their oxidized forms which may be methionine sulfoxide or methionine sulfone, or in the alternative may be substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl or saturated chains of 2 to 8 carbon atoms which may be branched or unbranched, wherein the aliphatic substituents may be substituted with an aromatic or heteroaromatic ring;

20

- 17 -

R⁴ is hydrogen or an alkyl group, wherein the alkyl group comprises straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms;

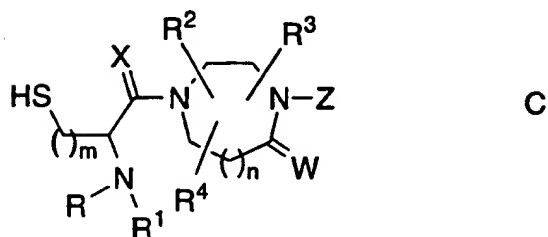
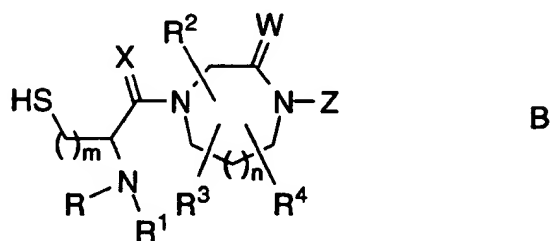
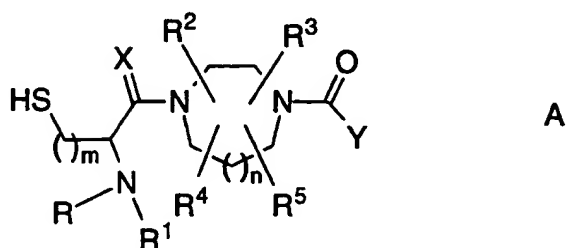
5 R⁶ is a substituted or unsubstituted aliphatic, aromatic or heteroaromatic group such as saturated chains of 1 to 8 carbon atoms, which may be branched or unbranched, wherein the aliphatic substituent may be substituted with an aromatic or heteroaromatic ring;

10

T is O or S(O)_m;
m is 0, 1 or 2; and
n is 0, 1 or 2;

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1) PCT Publication WO 95/00497, incorporated herein by reference,

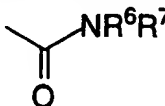
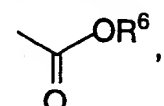


wherein:

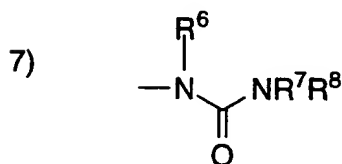
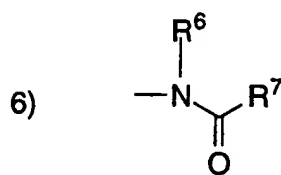
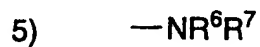
- 5 X is O or H₂;
 m is 1 or 2;
 n is 0 or 1;
 t is 1 to 4;
 R and R¹ are independently selected from H, C₁₋₄ alkyl, or aralkyl;

- 19 -

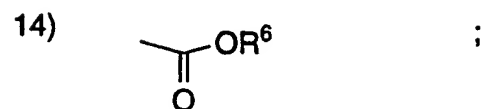
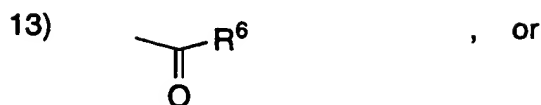
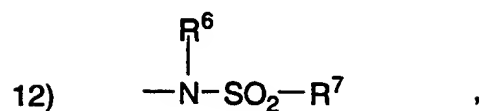
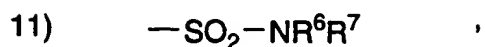
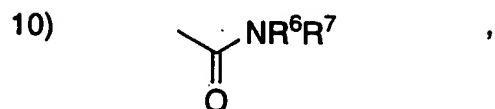
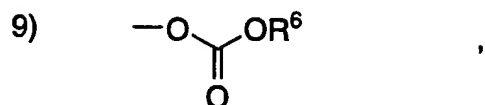
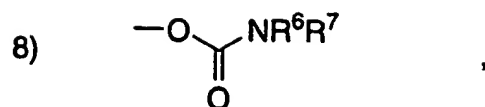
R^2, R^3, R^4 , and R^5 are independently selected from: H; C₁-8 alkyl, alkenyl,

alkynyl, aryl, heterocycle,  or , unsubstituted or substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) C₁-4 alkyl,
 - b) $(CH_2)_tOR^6$,
 - c) $(CH_2)_tNR^6R^7$,
 - d) halogen,
- 2) C₃-6 cycloalkyl,
- 3) OR^6 ,
- 4) $SR^6, S(O)R^6, SO_2R^6$,



- 20 -



and any two of R^2 , R^3 , R^4 , and R^5 are optionally attached to the same carbon atom;

5

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

10

1) C₁₋₄ alkyl, unsubstituted or substituted with:

- a) C₁₋₄ alkoxy,
- b) NR^6R^7 ,
- c) C₃₋₆ cycloalkyl,
- d) aryl or heterocycle,
- e) HO,

15

- 2) aryl or heterocycle,
- 3) halogen,
- 4) OR^6 ,

- 21 -

- 5) NR^6R^7 ,
- 6) CN ,
- 7) NO_2 , or
- 8) CF_3 ;

5

W is H_2 or O;

Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

10

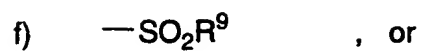
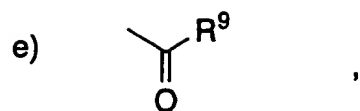
- 1) C_{1-4} alkyl, unsubstituted or substituted with:
 - a) C_{1-4} alkoxy,
 - b) NR^6R^7 ,
 - c) C_{3-6} cycloalkyl,
- 15 d) aryl or heterocycle, or
- e) HO ,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) OR^6 ,
- 20 5) NR^6R^7 ,
- 6) CN ,
- 7) NO_2 , or
- 8) CF_3 ;

25 R^6 , R^7 and R^8 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

30

- a) C_{1-4} alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO ,

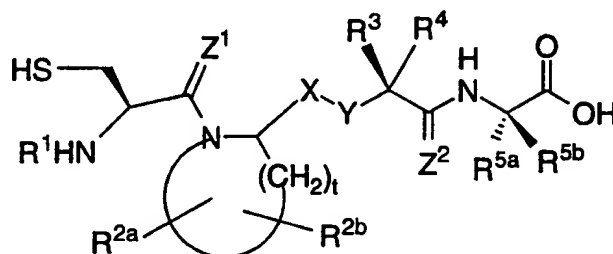
- 22 -



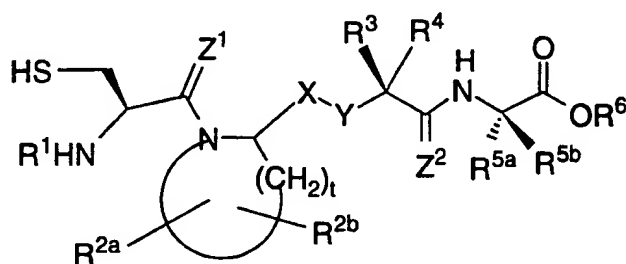
g) NRR^1 , wherein

- 5 R^6 and R^7 may be joined in a ring, and
 R^7 and R^8 may be joined in a ring; and
 R^9 is C1-4 alkyl or aralkyl;

- m) PCT Publication WO 96/09821 and U.S. Serial No. 08/315,059,
 10 incorporated herein by reference,

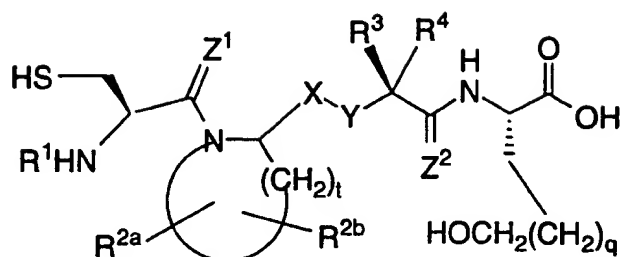
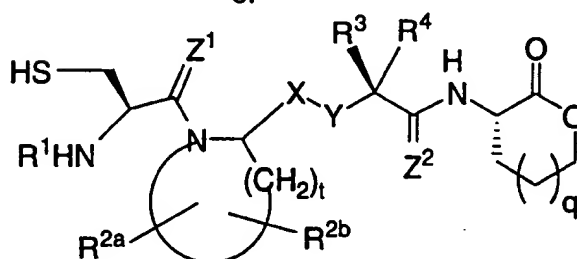


I



II

- 23 -

III
or

IV

wherein:

R¹ is selected from:

- a) hydrogen,
- b) R⁸S(O)₂-, R⁸C(O)-, (R⁸)₂NC(O)- or R⁹OC(O)-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, R⁸O-, R⁸S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

R^{2a} and R^{2b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R⁸O-, R⁸S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-,
- c) aryl, heterocycle, cycloalkyl, alkenyl, R⁸O-, R⁸S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and

- 24 -

d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

5 R³ and R⁴ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - 10 ii) methionine sulfone, and
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group, wherein the substituent is selected from F, Cl, Br, N(R⁸)₂, NO₂, R⁸O-, R⁸S(O)_m-,
15 R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-,
R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂,
R⁹OC(O)NR⁸- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-
20 C₁₀ cycloalkyl; or

R³ and R⁴ are combined to form - (CH₂)_s - ;

R^{5a} and R^{5b} are independently selected from:

- 25 a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone,
- 30 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group, wherein the substituent is selected from F, Cl, Br, N(R⁸)₂, NO₂, R⁸O-, R⁸S(O)_m-, R⁸C(O)NR⁸-, CN,

- 25 -

$(R^8)_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3 , $-N(R^8)_2$,
 $R^9OC(O)NR^8-$ and C_1-C_{20} alkyl, and

d) C_1-C_6 alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocyclic and C_3-
 C_{10} cycloalkyl; or

5

R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of
 the carbon atoms is optionally replaced by a moiety selected
 from: O, $S(O)_m$, $-NC(O)-$, and $-N(COR^8)-$;

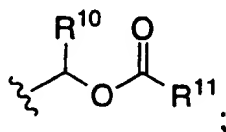
10 R^6 is

a) substituted or unsubstituted C_1-C_8 alkyl, wherein the
 substituent on the alkyl is selected from:

- 1) aryl,
- 2) heterocycle,
- 3) $-N(R^9)_2$,
- 4) $-OR^8$, or

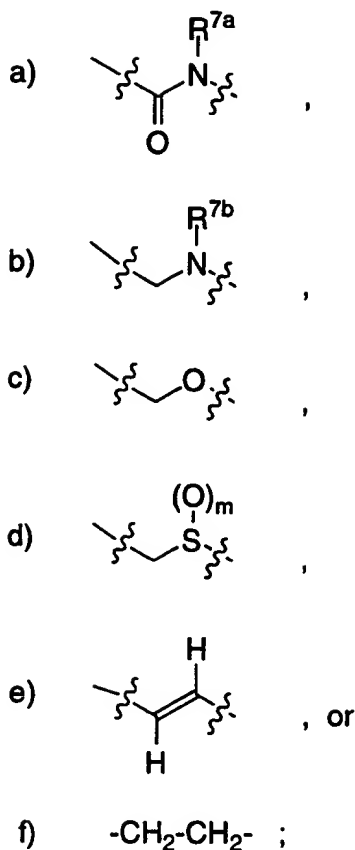
15

b)



- 26 -

X-Y is

R^{7a} is selected from

- 5 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted cycloalkyl, and
 e) C₁-C₆ alkyl substituted with hydrogen or an
 10 unsubstituted or substituted group selected from aryl,
 heterocycle and cycloalkyl;

R^{7b} is selected from

- a) hydrogen,
 15 b) unsubstituted or substituted aryl,

- 27 -

- 5 c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted cycloalkyl,
e) C₁-C₆ alkyl substituted with hydrogen or an
unsubstituted or substituted group selected from aryl,
heterocycle and cycloalkyl,
f) a carbonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocycle,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
an unsubstituted or substituted group selected from aryl,
10 heterocycle and cycloalkyl, and
g) a sulfonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocycle,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
an unsubstituted or substituted group selected from aryl,
15 heterocycle and cycloalkyl;

R⁸ is independently selected from hydrogen, C₁-C₆ alkyl and aryl;

20 R⁹ is independently selected from C₁-C₆ alkyl and aryl;

R¹⁰ is independently selected from hydrogen and C₁-C₆ alkyl;

R¹¹ is independently selected from C₁-C₆ alkyl;

25 Z¹ and Z² are independently H₂ or O, provided that Z¹ is not O when
X-Y is - C(O)N(R^{7a})-;

m is 0, 1 or 2;

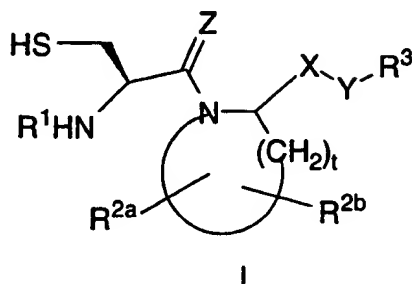
q is 0, 1 or 2;

30 s is 4 or 5; and

t is 3, 4 or 5;

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n) PCT Publication WO 96/09820 and U.S. Serial No. 08/315,151, incorporated herein by reference,



5 wherein:

R¹ is selected from:

- a) hydrogen,
 - b) R⁵S(O)₂-, R⁵C(O)-, (R⁵)₂NC(O)- or R⁶OC(O)-, and
 - c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
- 10 heterocyclic, cycloalkyl, alkenyl, alkynyl, R⁵O-,
R⁵S(O)_m-, R⁵C(O)NR⁵-, CN, (R⁵)₂N-C(NR⁵)-,
R⁵C(O)-, R⁵OC(O)-, N₃, -N(R⁵)₂, or R⁶OC(O)NR⁵-;

R^{2a} and R^{2b} are independently selected from:

- a) hydrogen,
 - b) C₁-C₆ alkyl unsubstituted or substituted by aryl,
- 15 heterocycle, cycloalkyl, alkenyl, R⁵O-, R⁵S(O)_m-,
R⁵C(O)NR⁵-, CN, (R⁵)₂N-C(NR⁵)-, R⁵C(O)-,
R⁵OC(O)-, N₃, -N(R⁵)₂, or R⁶OC(O)NR⁵-, and
- c) aryl, heterocycle, cycloalkyl, alkenyl, R⁵O-, R⁵S(O)_m-,
- 20 R⁵C(O)NR⁵-, CN, NO₂, (R⁵)₂N-C(NR⁵)-, R⁵C(O)-,
R⁵OC(O)-, N₃, -N(R⁵)₂, or R⁶OC(O)NR⁵-,

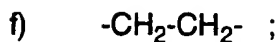
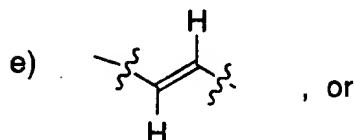
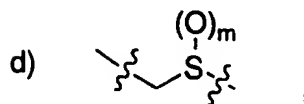
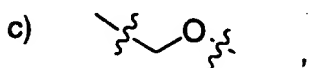
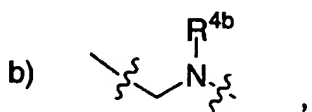
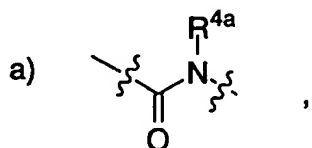
R³ is selected from:

- a) unsubstituted or substituted aryl,
 - b) unsubstituted or substituted heterocycle,
 - c) unsubstituted or substituted cycloalkyl, and
- 25

- 29 -

d) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl;

X-Y is



R^{4a} is selected from

10

- a) hydrogen,
- b) unsubstituted or substituted aryl,
- c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted cycloalkyl, and
- e) C₁-C₆ alkyl substituted with hydrogen or an

15

unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl;

- 30 -

R^{4b} is selected from

- a) hydrogen,
- b) unsubstituted or substituted aryl,
- 5 c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted cycloalkyl,
- e) C₁-C₆ alkyl substituted with hydrogen or an
unsubstituted or substituted group selected from aryl,
heterocycle and cycloalkyl,
- 10 f) a carbonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocycle,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
an unsubstituted or substituted group selected from aryl,
heterocycle and cycloalkyl, and
- 15 g) a sulfonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocycle,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
an unsubstituted or substituted group selected from aryl,
heterocycle and cycloalkyl;

20

R⁵ is independently selected from hydrogen, C₁-C₆ alkyl and aryl;

R⁶ is independently selected from C₁-C₆ alkyl and aryl;

25 Z is independently H₂ or O;

m is 0, 1 or 2, provided that m is 0 when R⁵ = hydrogen ;

n is 0, 1, 2, 3 or 4; and

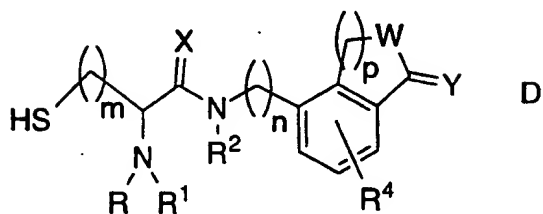
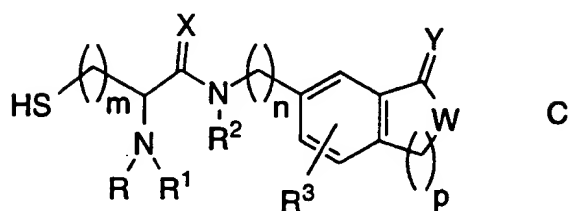
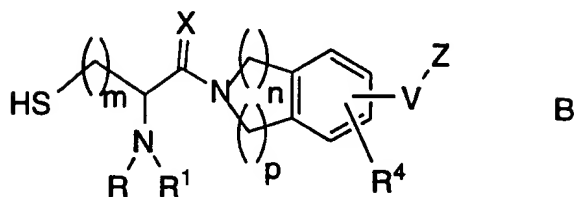
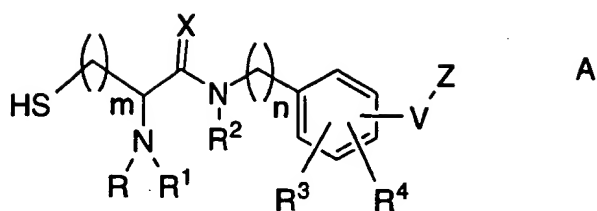
t is 3, 4 or 5;

30

and

p) U.S. Serial Nos. 08/412,621 and 08/448,856, incorporated herein by
reference,

- 31 -



wherein:

X and Y are independently O or H₂;

- 5 m is 1 or 2;
 n is 0 or 1;
 p is 1, 2 or 3;
 q is 0, 1 or 2;
 t is 1 to 4;
- 10 R, R¹ and R² are independently selected from: H, C₁-6 alkyl, or C₁-6
 aralkyl;
 R³ and R⁴ are independently selected from:

- 32 -

- 5 a) hydrogen,
 b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, R⁶O-, R⁵S(O)_q-, R⁷C(O)NR⁶-, CN, N₃, R⁶OC(O)NR⁶-, R⁶R⁷N-C(NR⁶R⁸)-, R⁶C(O)-, R⁷R⁸NC(O)O-, R⁷R⁸NC(O)-, R⁶R⁷N-S(O)₂-, -NR⁶S(O)₂R⁵, R⁶OC(O)O-, -NR⁶R⁷, or R⁷R⁸NC(O)NR⁶-,
 c) unsubstituted or substituted cycloalkyl, alkenyl, R⁶O-, R⁵S(O)_q-, R⁶C(O)NR⁶-, CN, NO₂, R⁶R⁷N-C(NR⁸)-, R⁶C(O)-, N₃, -NR⁶R⁷,
 10 halogen or R⁷OC(O)NR⁶-, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

15 W is -CHR⁹- or -NR⁹- ;

Z is unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle;

20 wherein the substituted group is substituted with one or more of:

- 1) C₁-4 alkyl, unsubstituted or substituted with:
 a) C₁-4 alkoxy,
 b) NR⁶R⁷,
 c) C₃-6 cycloalkyl,
 25 d) aryl or heterocycle,
 e) HO,
 2) aryl or heterocycle,
 3) halogen,
 4) OR⁶,
 30 5) NR⁶R⁷,
 6) CN,
 7) NO₂, or
 9) CF₃;

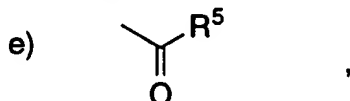
- 33 -

R^5 is C₁₋₄ alkyl or aralkyl;

R^6 , R^7 and R^8 are independently selected from: H, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl,

5 heteroarylsulfonyl, unsubstituted or substituted with:

- a) C₁₋₄ alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO,



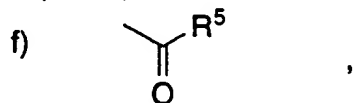
- 10 f) $-\text{SO}_2\text{R}^5$, or
g) $-\text{NR}^6\text{R}^7$, or

R^6 and R^7 may be joined in a ring, and
 R^7 and R^8 may be joined in a ring;

15

R^9 is selected from: H, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle and aryl, unsubstituted, monosubstituted or disubstituted with substituents independently selected from:

- 20 a) C₁₋₄ alkyl,
b) C₁₋₄ alkoxy,
c) aryl or heterocycle,
d) halogen,
e) HO,



- 25 g) $-\text{SO}_2\text{R}^5$, and
h) $-\text{NR}^6\text{R}^7$;

- 34 -

V is selected from: $-C(R^{11})=C(R^{11})-$, $-C\equiv C-$, $-C(O)-$, $-C(R^{11})_2-$,
5 $-C(OR^{11})R^{11}-$, $-CN(R^{11})_2R^{11}-$, $-OC(R^{11})_2-$, $-NR^{11}C(R^{11})_2-$,
 $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C(O)NR^{11}-$, $-NR^{11}C(O)-$, O,
 $-NC(O)R^{11}-$, $-NC(O)OR^{11}-$, $-S(O)_2N(R^{11})-$, $-N(R^{11})S(O)_2-$, or
S(O)_m;

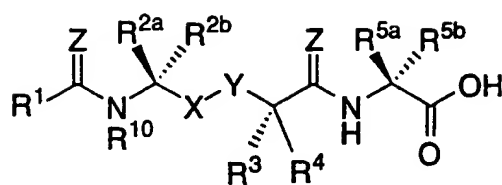
R¹⁰ and R¹¹ are independently selected from hydrogen, C₁-C₆ alkyl,
C₂-C₄ alkenyl, benzyl and aryl;

10 or the pharmaceutically acceptable salt thereof.

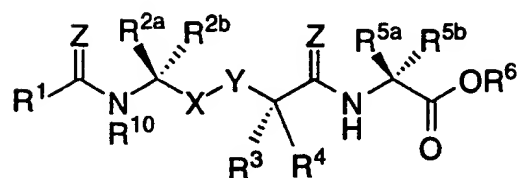
The composition of the instant invention may alternatively
or in addition comprise a protein substrate-competitive inhibitor that does
not incorporate a cysteinyl or sulfhydryl containing moiety at the N-
15 terminus of the molecule. The lack of a sulfhydryl offers unique
advantages in terms of improved pharmacokinetic behavior in animals,
prevention of thiol-dependent chemical reactions, such as rapid
autoxidation and disulfide formation with endogenous thiols, and reduced
systemic toxicity. Thus the following compounds, well known in the art,
20 are also useful as protein substrate-competitive inhibitors in the instant
invention:

q) PCT Publication WO 95/09001 and U.S. Serial No. 08/314,987,
incorporated herein by reference,

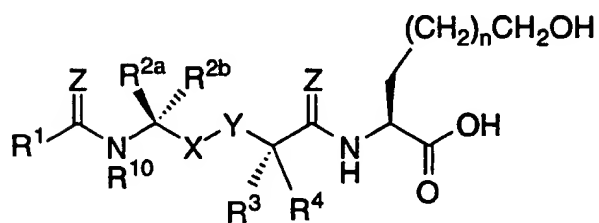
- 35 -



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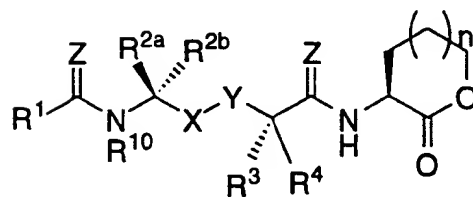


II



III

or



IV

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R¹ is selected from:

- 5 a) heterocycle, and
 b) C₁-C₁₀ alkyl, which is substituted with heterocycle and
 which is optionally substituted with one or more of C₁-C₄
 alkyl, hydroxy or amino groups;

R^{2a} and R^{2b} are independently selected from:

- 10 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally
 occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀
 alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
15 wherein the substituent is selected from F, Cl, Br,
 NO₂, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-
 C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂,
 R⁹OC(O)NR⁸- and C₁-C₂₀ alkyl, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or
20 substituted group selected from aryl, heterocycle and C₃-
 C₁₀ cycloalkyl; or

R^{2a} and R^{2b} are combined to form - (CH₂)_s - ;

25 R³ and R⁴ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring
 amino acid which is:
 i) methionine sulfoxide, or
30 ii) methionine sulfone, and
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀
 alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 N(R⁸)₂, NO₂, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-,

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5 CN, $(R^8)_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3 ,
- $N(R^8)_2$, $R^9OC(O)NR^8-$ and C₁-C₂₀ alkyl,, and
d) C₁-C₆ alkyl substituted with an unsubstituted or
substituted group selected from aryl, heterocyclic and C₃-
C₁₀ cycloalkyl; or

R^3 and R^4 are combined to form $-(CH_2)_s-$;

R^{5a} and R^{5b} are independently selected from:

- 10 a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring
amino acid which is:
i) methionine sulfoxide, or
ii) methionine sulfone,
15 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀
alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
wherein the substituent is selected from F, Cl, Br,
 $N(R^8)_2$, NO_2 , R^8O- , $R^9S(O)_m-$, $R^8C(O)NR^8-$,
CN, $(R^8)_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3 ,
20 - $N(R^8)_2$, $R^9OC(O)NR^8-$ and C₁-C₂₀ alkyl, and
d) C₁-C₆ alkyl substituted with an unsubstituted or
substituted group selected from aryl, heterocyclic and C₃-
C₁₀ cycloalkyl; or

25 R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of the
carbon atoms is optionally replaced by a moiety selected from: O,
 $S(O)_m$, $-NC(O)-$, and $-N(COR^8)-$;

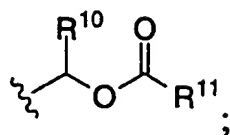
R^6 is

- 30 a) substituted or unsubstituted C₁-C₈ alkyl, wherein the
substituent on the alkyl is selected from:
1) aryl,
2) heterocycle,
3) $-N(R^9)_2$,

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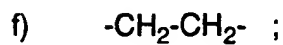
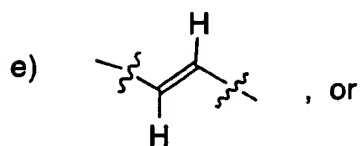
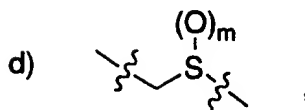
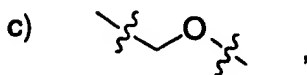
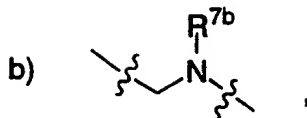
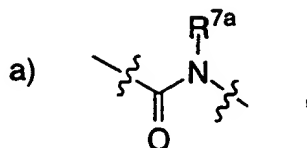
4) -OR⁸, or

b)



5

X-Y is



10

R^{7a} is selected from

- a) hydrogen,
- b) unsubstituted or substituted aryl,
- c) unsubstituted or substituted heterocyclic,

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- d) unsubstituted or substituted cycloalkyl, and
- e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocyclic and cycloalkyl;

5

R^{7b} is selected from

- a) hydrogen,
- b) unsubstituted or substituted aryl,
- c) unsubstituted or substituted heterocyclic,
- 10 d) unsubstituted or substituted cycloalkyl,
- e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocyclic and cycloalkyl,
- f) a carbonyl group which is bonded to an unsubstituted or
- 15 substituted group selected from aryl, heterocyclic, cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocyclic and cycloalkyl, and
- g) a sulfonyl group which is bonded to an unsubstituted or
- 20 substituted group selected from aryl, heterocyclic, cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocyclic and cycloalkyl;

25 R⁸ is independently selected from hydrogen, C₁-C₆ alkyl and aryl;

R⁹ is independently selected from C₁-C₆ alkyl and aryl;

R¹⁰ is independently selected from hydrogen and C₁-C₆ alkyl;

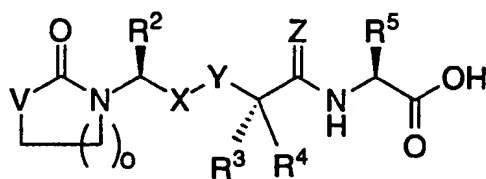
30

R¹¹ is independently selected from C₁-C₆ alkyl;

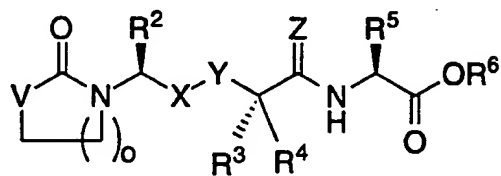
Z is independently H₂ or O;

**m is 0, 1 or 2;
n is 0, 1 or 2; and
s is 4 or 5;**

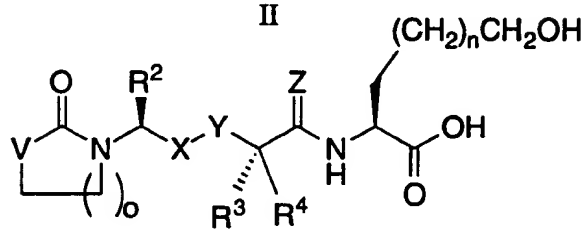
5 r) PCT Publication WO 95/09000 and U.S. Pat. No. 5,468,773,
incorporated herein by reference,



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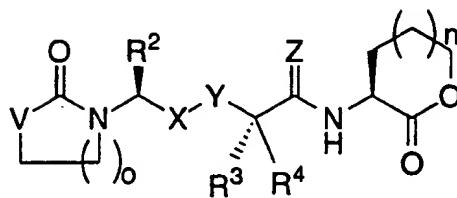


II



III

and



IV

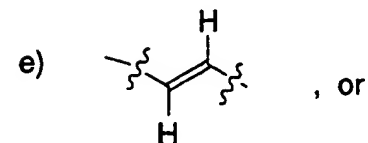
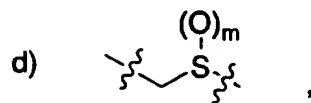
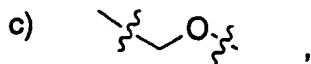
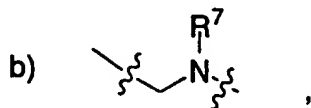
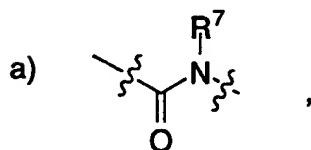
wherein:

V is CH₂, O, S, HN, or R⁷N;

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5 R², R³, R⁴ and R⁵ are independently the side chains of naturally
 occurring amino acids, including their oxidized forms
 which may be methionine sulfoxide or methionine sulfone,
 or in the alternative may be substituted or unsubstituted
 aliphatic, aromatic or heteroaromatic groups, such as allyl,
 cyclohexyl, phenyl, pyridyl, imidazolyl or saturated chains
 of 2 to 8 carbon atoms which may be branched or
 10 unbranched, wherein the aliphatic substituents may be
 substituted with an aromatic or heteroaromatic ring;

X-Y is

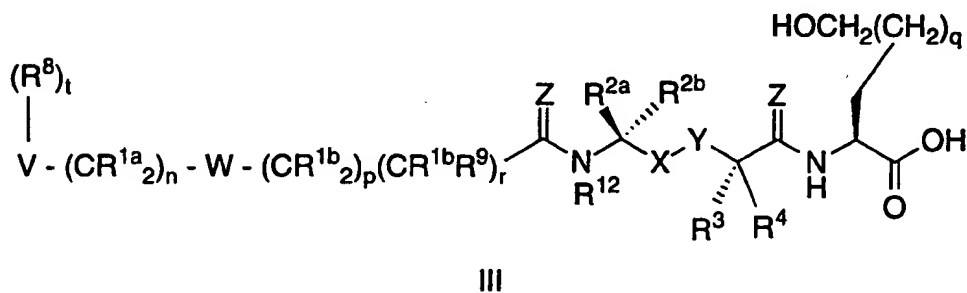
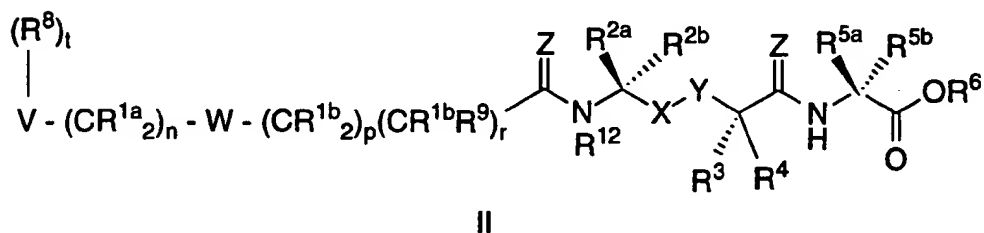
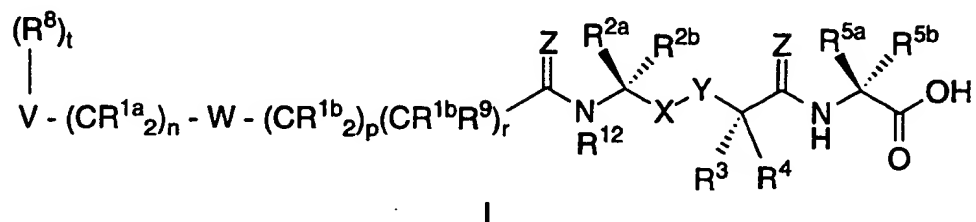


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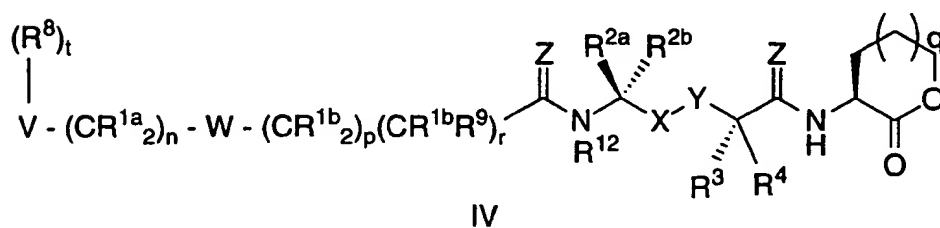
- 5 **R⁶** is a substituted or unsubstituted aliphatic, aromatic or heteroaromatic group such as saturated chains of 1 to 8 carbon atoms, which may be branched or unbranched, wherein the aliphatic substituent may be substituted with an aromatic or heteroaromatic ring;
- 10 **R⁷** is an alkyl group, wherein the alkyl group comprises straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms, which may be substituted with an aromatic or heteroaromatic group;
- 15 **Z** is H₂ or O;
 m is 0, 1 or 2;
 n is 0, 1 or 2; and
 o is 0, 1, 2 or 3;

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s) PCT Publication WO 96/09836 and U.S. Serial No. 08/315,171, incorporated herein by reference,



and



wherein:

5 R^{1a} is selected from:

- a) hydrogen,
- b) aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, or R¹⁰OC(O)-, and

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- 5 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R^{1b} is independently selected from:

- 10 a) hydrogen,
 b) unsubstituted or substituted aryl, cycloalkyl, alkenyl, alkynyl, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, or R¹⁰OC(O)-, and
 15 c) C₁-C₆ alkyl unsubstituted or substituted by unsubstituted or substituted aryl, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;
 provided that R^{1b} is not R¹⁰C(O)NR¹⁰- when R^{1a} is alkenyl, V is hydrogen and X-Y is -C(O)NR^{7a}-;

20 R^{2a} and R^{2b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 25 i) methionine sulfoxide, or
 ii) methionine sulfone,
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group, wherein the substituent is selected from F, Cl, Br, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 30 -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

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R^{2a} and R^{2b} are combined to form - (CH₂)_s - ;

R³ and R⁴ are independently selected from:

- 5 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally
 occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
10 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀
 alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
15 -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and C₃-
 C₁₀ cycloalkyl; or

20 R³ and R⁴ are combined to form - (CH₂)_s - ;

R^{5a} and R^{5b} independently selected from:

- a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally
25 occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀
 alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
30 wherein the substituent is selected from F, Cl, Br,
 NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and

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d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

5 R_{5a} and R_{5b} are combined to form - (CH₂)_s - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

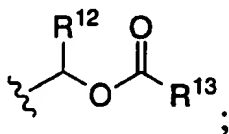
R⁶ is

10 a) substituted or unsubstituted C₁-C₈ alkyl, wherein the substituent on the alkyl is selected from:

- 1) aryl,
- 2) heterocycle,
- 3) -N(R¹¹)₂,
- 4) -OR¹⁰, or

15

b)



- 48 -

- c) unsubstituted or substituted heterocyclic,
- d) unsubstituted or substituted cycloalkyl,
- e) C₁-C₆ alkyl substituted with hydrogen or an
 5 unsubstituted or substituted group selected from aryl,
 heterocyclic and cycloalkyl,
- f) a carbonyl group which is bonded to an unsubstituted
 or substituted group selected from aryl, heterocyclic,
 cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
 an unsubstituted or substituted group selected from aryl,
 10 heterocyclic and cycloalkyl, and
- g) a sulfonyl group which is bonded to an unsubstituted
 or substituted group selected from aryl, heterocyclic,
 cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
 an unsubstituted or substituted group selected from aryl,
 15 heterocyclic and cycloalkyl;

R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl,
 20 perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
 R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-,
 R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 25 heterocyclic, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl,
 F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-
 C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NH-;

30 R⁹ is selected from:

- hydrogen, C₁-C₆ alkyl, R¹⁰O-, R¹¹S(O)_m-,
 R¹⁰C(O)NR¹⁰-, CN, NO₂, N₃, -N(R¹⁰)₂, and
 R¹¹OC(O)NR¹⁰-;

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provided that R^9 is not $R^{10}C(O)NR^{10}$ - when R^{1a} is alkenyl, V is hydrogen and X-Y is $-C(O)NR^{7a}$;

5 R^{10} is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R^{11} is independently selected from C₁-C₆ alkyl and aryl;

10 R^{12} is independently selected from hydrogen and C₁-C₆ alkyl;

R^{13} is C₁-C₆ alkyl;

V is selected from:

- 15 a) aryl;
b) heterocycle; or
c) hydrogen;

20 W is $-S(O)_m-$, $-O-$, $-NHC(O)-$, $-C(O)NH-$, $-NH SO_2-$, $-SO_2NH-$, $-N(R^{7a})-$ or $-N[C(O)R^{7a}]-$;

Z is independently H₂ or O;

m is 0, 1 or 2;

25 n is 0, 1, 2, 3 or 4, provided that $n \neq 0$ when V is hydrogen and W is $-S(O)_m-$;

p is 0, 1, 2, 3 or 4, provided that $p \neq 0$ when R^9 is not hydrogen or C₁-C₆ lower alkyl ;

q is 0, 1 or 2;

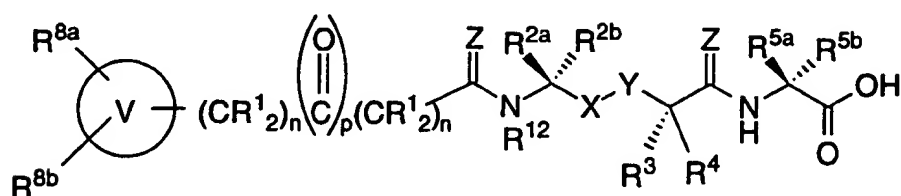
30 r is 0 or 1;

s is 4 or 5; and

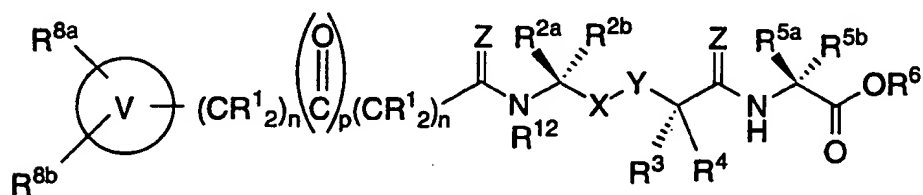
t is 0, 1 or 2, provided that $t = 0$ when V is hydrogen;

- 50 -

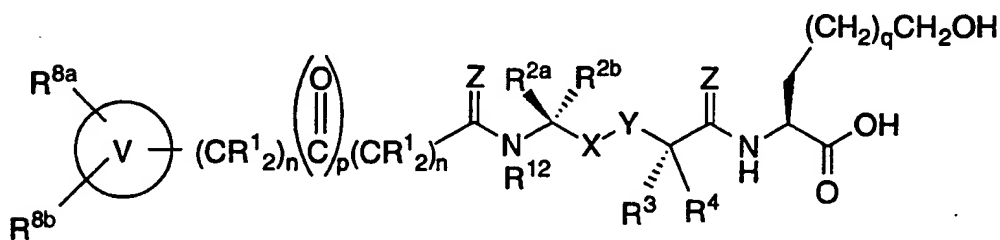
t) PCT Publication WO 96/10011 and U.S. Serial No. 08/315,046, incorporated herein by reference,



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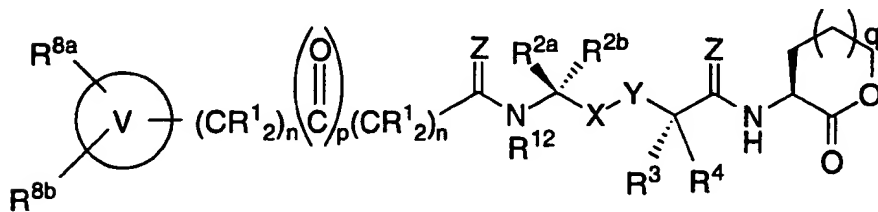


II



III

and



IV

5 wherein:

R¹ is hydrogen, C₁-C₆ alkyl or aryl;

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R2a and R2b are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - 5 i) methionine sulfoxide, or
 - ii) methionine sulfone,
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
wherein the substituent is selected from F, Cl, Br,
10 NO₂, R⁹O-, R¹⁰S(O)_m-, R⁹C(O)NR⁹-, CN, (R⁹)₂N-
C(NR⁹)-, R⁹C(O)-, R⁹OC(O)-, N₃, -N(R⁹)₂,
R¹⁰OC(O)NR⁹- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or
substituted group selected from aryl, heterocycle and
15 C₃-C₁₀ cycloalkyl; or

R2a and R2b are combined to form - (CH₂)_s - ;

R3 and R4 are independently selected from:

- 20 a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone,
- 25 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
wherein the substituent is selected from F, Cl, Br,
NO₂, R⁹O-, R¹⁰S(O)_m-, R⁹C(O)NR⁹-, CN, (R⁹)₂N-
C(NR⁹)-, R⁹C(O)-, R⁹OC(O)-, N₃, -N(R⁹)₂,
30 R¹⁰OC(O)NR⁹- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or
substituted group selected from aryl, heterocycle and C₃-
C₁₀ cycloalkyl; or

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R³ and R⁴ are combined to form - (CH₂)_s - ;

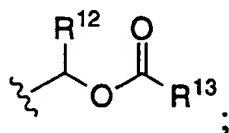
R^{5a} and R^{5b} are independently selected from:

- 5 a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone,
- 10 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group, wherein the substituent is selected from F, Cl, Br, NO₂, R⁹O-, R¹⁰S(O)_m-, R⁹C(O)NR⁹-, CN, (R⁹)₂N-C(NR⁹)-, R⁹C(O)-, R⁹OC(O)-, N₃, -N(R⁹)₂, R¹⁰OC(O)NR⁹- and C₁-C₂₀ alkyl, and
- 15 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

20 R^{5a} and R^{5b} are combined to form - (CH₂)_s - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR⁹)- ;

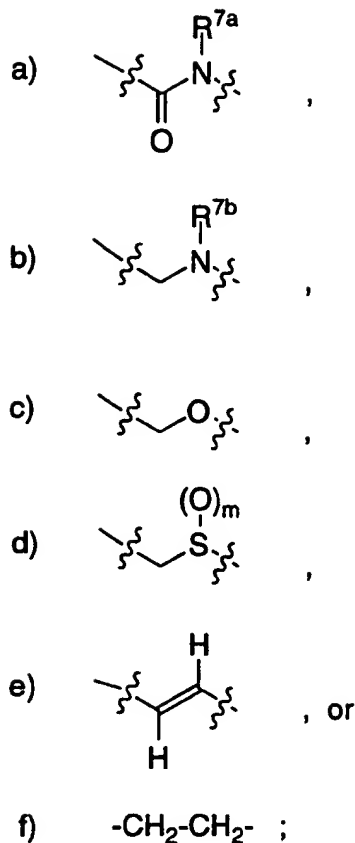
R⁶ is

- 25 a) substituted or unsubstituted C₁-C₈ alkyl, wherein the substituent on the alkyl is selected from:
 - 1) aryl,
 - 2) heterocycle,
 - 3) -N(R¹⁰)₂,
 - 4) -OR⁹, or
- 30 b)



- 53 -

X-Y is

R^{7a} is selected from

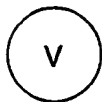
- 5 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted cycloalkyl, and
 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted
 10 or substituted group selected from aryl, heterocycle and
 cycloalkyl;

R^{7b} is selected from

- 15 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted cycloalkyl,

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- e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl,
- 5 f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl, and
- 10 g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl;
- 15 R^{8a} and R^{8b} are independently selected from:
hydrogen, F, Cl, Br, NO₂, R¹¹O-, R¹⁰S(O)_m-, CN,
R⁹C(O)NR⁹-, (R⁹)₂N-C(NR⁹)-, R⁹C(O)-, R⁹OC(O)-,
N₃, -N(R⁹)₂, R¹⁰OC(O)NR⁹-, C₁-C₂₀ alkyl, aryl,
20 heterocycle or C₁-C₂₀ alkyl substituted with aryl or heterocycle;
- R⁹ is independently selected from hydrogen, C₁-C₆ alkyl and aryl;
- R¹⁰ is independently selected from C₁-C₆ alkyl and aryl;
- 25 R¹¹ is independently selected from hydrogen, C₁-C₆ alkyl and aryl,
provided R¹¹ is C₁-C₆ alkyl when n is 0;
- R¹² is independently hydrogen or C₁-C₆ alkyl;
- 30 R¹³ is C₁-C₆ alkyl;



is aryl or 1,2,3,4-tetrahydronaphthyl;

- 55 -

Z is independently H₂ or O;

m is 0, 1 or 2;

5 n is independently 0 to 4;

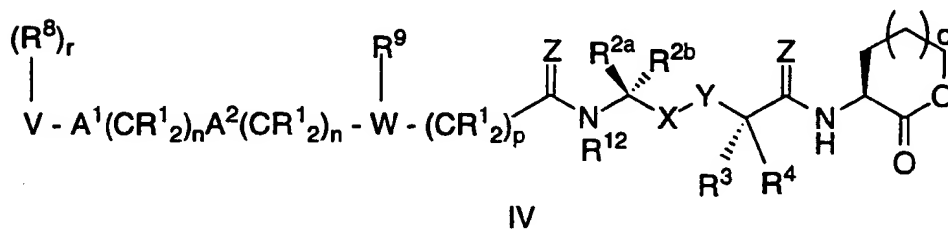
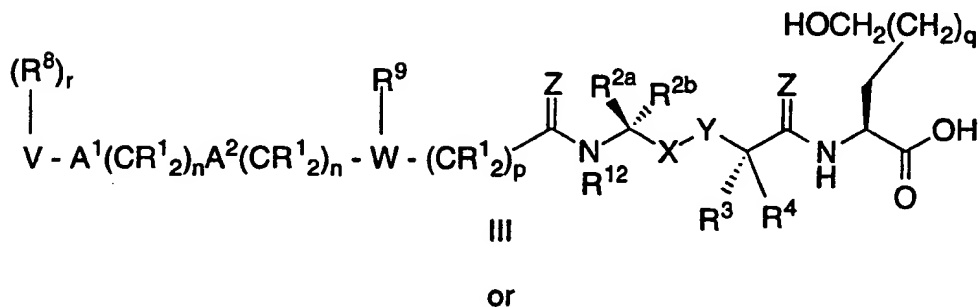
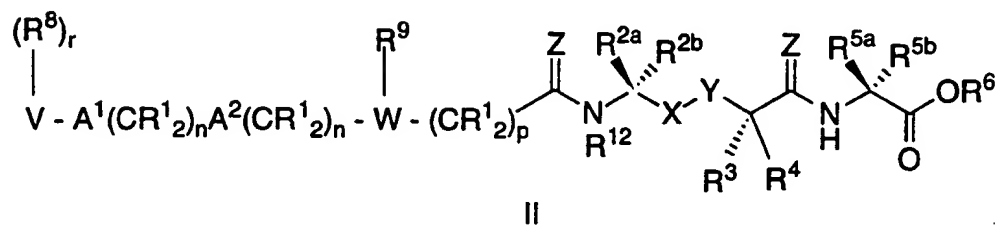
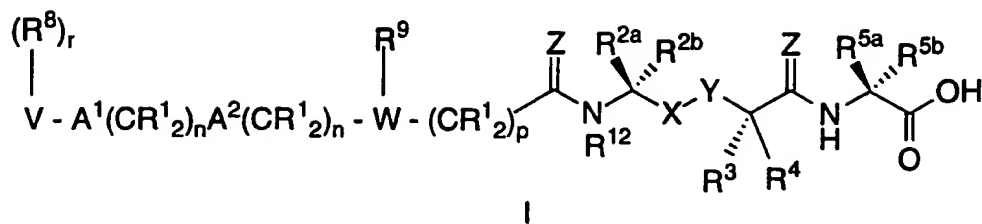
p is 0 or 1;

q is 0, 1 or 2; and

s is 4 or 5;

10 u) PCT Publication WO 96/10034 and U.S. Serial No. 08/314,974,
incorporated herein by reference,

- 56 -



wherein:

 R^1 is independently selected from:

- 5 a) hydrogen,
- b) aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- 10 c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$,

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$R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or
 $R^{11}OC(O)NR^{10}-$;

R^{2a} and R^{2b} are independently selected from:

- 5 a) a side chain of a naturally occurring amino acid,
 - b) an oxidized form of a side chain of a naturally
 occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone,
 - 10 c) substituted or unsubstituted C_1 - C_{20} alkyl, C_2 - C_{20}
 alkenyl, C_3 - C_{10} cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN,
 $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 ,
 - 15 $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1 - C_{20} alkyl, and
 - d) C_1 - C_6 alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and C_3 -
 C_{10} cycloalkyl; or
- 20 R^{2a} and R^{2b} are combined to form $-(CH_2)_s-$;

R^3 and R^4 are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally
- 25 occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone,
- c) substituted or unsubstituted C_1 - C_{20} alkyl, C_2 - C_{20}
 alkenyl, C_3 - C_{10} cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
- 30 $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$,
 CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 ,
 $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1 - C_{20} alkyl, and

- 58 -

d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

5 R³ and R⁴ are combined to form - (CH₂)_s - ;

R^{5a} and R^{5b} are independently selected from:

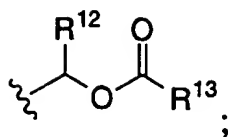
- 10 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally
 occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀
 alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
15 wherein the substituent is selected from F, Cl, Br,
 N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
20 d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and C₃-
 C₁₀ cycloalkyl; or

25 R^{5a} and R^{5b} are combined to form - (CH₂)_s - wherein one of
 the carbon atoms is optionally replaced by a moiety selected
 from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

R⁶ is

- 30 a) substituted or unsubstituted C₁-C₈ alkyl, wherein the
 substituent on the alkyl is selected from:
 1) aryl,
 2) heterocycle,
 3) -N(R¹¹)₂,
 4) -OR¹⁰, or
 b)

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X-Y is

- a) ,
- b) ,
- c) ,
- d) ,
- e) , or
- f) $-\text{CH}_2-\text{CH}_2-$;

5

R^{7a} is selected from

- a) hydrogen,
- b) unsubstituted or substituted aryl,
- c) unsubstituted or substituted heterocyclic,
- d) unsubstituted or substituted cycloalkyl, and
- e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocyclic and cycloalkyl;

10

- 60 -

R^{7b} is selected from

- a) hydrogen,
- b) unsubstituted or substituted aryl,
- 5 c) unsubstituted or substituted heterocyclic,
- d) unsubstituted or substituted cycloalkyl,
- e) C₁-C₆ alkyl substituted with hydrogen or an
unsubstituted or substituted group selected from aryl,
heterocyclic and cycloalkyl,
- 10 f) a carbonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocyclic,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
an unsubstituted or substituted group selected from aryl,
heterocyclic and cycloalkyl, and
- 15 g) a sulfonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocyclic,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
an unsubstituted or substituted group selected from aryl,
heterocyclic and cycloalkyl;

20

R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl,
perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
25 R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-,
R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
heterocyclic, cycloalkyl, alkenyl, alkynyl,
30 perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-,
R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NH-;

30

R⁹ is selected from:

- 61 -

- a) hydrogen,
 b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O-$,
 $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 , $(R^{10})_2N-$
 $C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or
 5 $R^{11}OC(O)NR^{10}-$, and
 c) C_1 - C_6 alkyl unsubstituted or substituted by
 perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$,
 $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$,
 $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;
 10 R^{10} is independently selected from hydrogen, C_1 - C_6 alkyl and aryl;
 R^{11} is independently selected from C_1 - C_6 alkyl and aryl;
 15 R^{12} is independently selected from hydrogen and C_1 - C_6 alkyl;
 R^{13} is independently selected from C_1 - C_6 alkyl;
 A^1 and A^2 are independently selected from: a bond, $-CH=CH-$,
 20 $-C\equiv C-$, $-C(O)-$, $-C(O)NR^{10}-$, O, $-N(R^{10})-$,
 $-NR^{10}C(O)-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$ or $S(O)_m$;
 V is selected from:
 a) hydrogen,
 25 b) heterocycle,
 c) aryl,
 d) C_1 - C_{20} alkyl wherein from 0 to 4 non-terminal
 carbon atoms are replaced with a heteroatom selected
 from O, S, and N, and
 30 e) C_2 - C_{20} alkenyl ;
 provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not
 hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$ or a bond;

W is a heterocycle;

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Z is independently H₂ or O;

m is 0, 1 or 2;

5 n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

q is 0, 1 or 2;

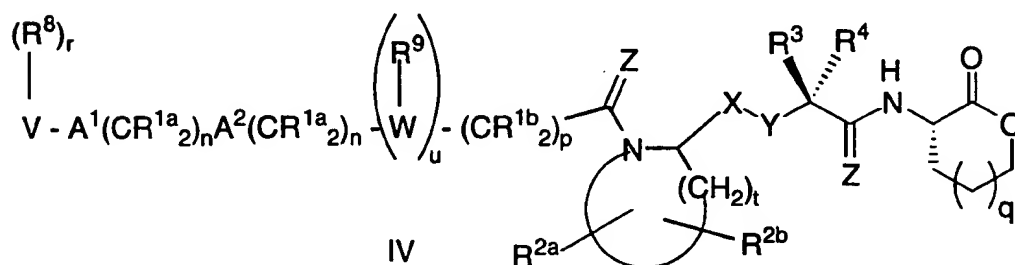
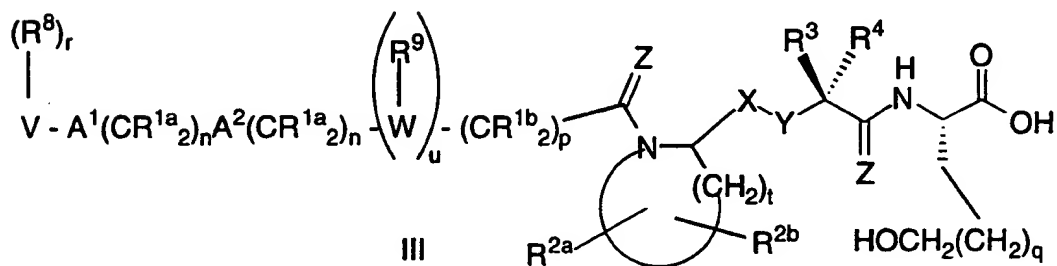
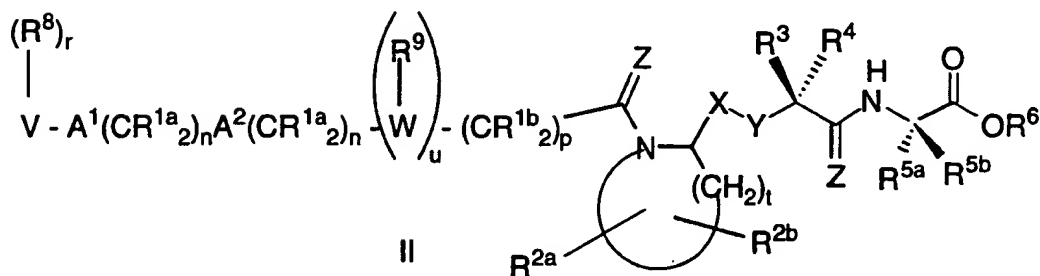
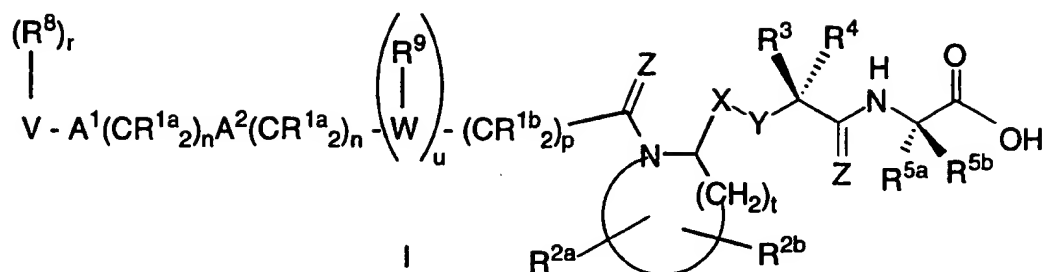
r is 0 to 5, provided that r is 0 when V is hydrogen; and

s is 4 or 5;

10

v) PCT Publication WO 96/10035 and U.S. Serial Nos. 08/315,161;
08/399,282; and 08/472,077, incorporated herein by reference,

- 63 -



wherein:

R^{1a} and R^{1b} are independently selected from:

- 5 a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂,

- 64 -

$(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 ,
 $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,

- 5 c) C1-C6 alkyl unsubstituted or substituted by aryl,
 heterocyclic, C3-C10 cycloalkyl, C2-C6 alkenyl, C2-C6
 alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN,
 $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$,
 or $R^{11}OC(O)-NR^{10}-$;

R2a and R2b are independently selected from:

- 10 a) hydrogen,
 b) C1-C6 alkyl unsubstituted or substituted by C2-C6 alkenyl,
 $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, N_3 , $(R^{10})_2N-$
 $C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or
 $R^{11}OC(O)NR^{10}-$,
 15 c) aryl, heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl, $R^{10}O-$,
 $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 , $(R^{10})_2N-C(NR^{10})-$,
 $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
 and
 d) C1-C6 alkyl substituted with an unsubstituted or
 20 substituted group selected from aryl, heterocyclic and
 C3-C10 cycloalkyl;

R3 and R4 are independently selected from:

- 25 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring
 amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
 c) substituted or unsubstituted C1-C20 alkyl, C2-C20 alkenyl,
 30 C3-C10 cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$,
 CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 ,
 $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C1-C20 alkyl, and

- 65 -

- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

5 R³ and R⁴ are combined to form - (CH₂)_s - ;

R^{5a} and R^{5b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring
10 amino acid which is:
i) methionine sulfoxide, or
ii) methionine sulfone,
c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl,
C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
15 wherein the substituent is selected from F, Cl, Br,
CF₃, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-,
R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-,
R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and
C₁-C₂₀ alkyl, and
20 d) C₁-C₆ alkyl substituted with an unsubstituted or
substituted group selected from aryl, heterocycle and C₃-
C₁₀ cycloalkyl; or

25 R^{5a} and R^{5b} are combined to form - (CH₂)_s - wherein one of the carbon
atoms is optionally replaced by a moiety selected from: O, S(O)_m,
-NC(O)-, and -N(COR¹⁰)- ;

R⁶ is

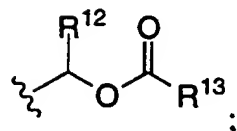
- a) substituted or unsubstituted C₁-C₈ alkyl, substituted or
30 unsubstituted C₅-C₈ cycloalkyl, or substituted or
unsubstituted cyclic amine, wherein the substituted alkyl,
cycloalkyl or cyclic amine is substituted with 1 or 2
substituents independently selected from:
1) C₁-C₆ alkyl,

- 66 -

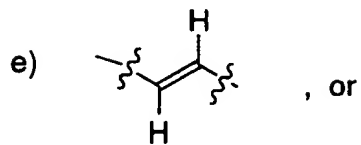
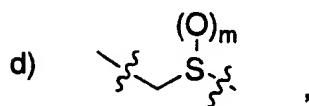
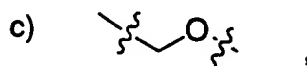
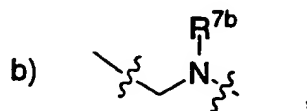
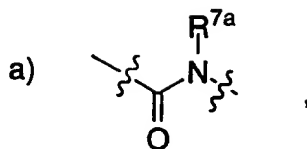
- 2) aryl,
- 3) heterocycle,
- 4) $-N(R^{11})_2$,
- 5) $-OR^{10}$, or

5

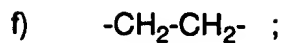
b)



X-Y is



10

R^{7a} is selected from

- a) hydrogen,
- b) unsubstituted or substituted aryl,

- 67 -

- 5 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted C₃-C₁₀ cycloalkyl, and
 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or
 substituted group selected from aryl, heterocycle and C₃-
 C₁₀ cycloalkyl;

R^{7b} is selected from

- 10 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or
 substituted group selected from aryl, heterocycle and C₃-
 C₁₀ cycloalkyl,
15 f) a carbonyl group which is bonded to an unsubstituted or
 substituted group selected from aryl, heterocycle, C₃-C₁₀
 cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an
 unsubstituted or substituted group selected from aryl,
 heterocycle and C₃-C₁₀ cycloalkyl, and
20 g) a sulfonyl group which is bonded to an unsubstituted or
 substituted group selected from aryl, heterocycle, C₃-C₁₀
 cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an
 unsubstituted or substituted group selected from aryl,
 heterocycle and C₃-C₁₀ cycloalkyl;

25

R⁸ is independently selected from:

- a) hydrogen,
 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆
 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
30 R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-,
 R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆
 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,

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$R^{10}C(O)NH-$, CN , $H_2N-C(NH)-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{10}OC(O)NH-$;

R^9 is selected from:

- 5 a) hydrogen,
- b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , NO_2 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$, and
- 10 c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;

- 15 R^{10} is independently selected from H, C_1-C_6 alkyl, benzyl, substituted aryl and C_1-C_6 alkyl substituted with substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

- 20 R^{12} is hydrogen or C_1-C_6 alkyl;

R^{13} is C_1-C_6 alkyl;

- 25 A^1 and A^2 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$, $-C(O)-$, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, O, $-N(R^{10})-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$, or $S(O)_m$;

V is selected from:

- 30 a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C_2-C_{20} alkenyl,

- 69 -

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

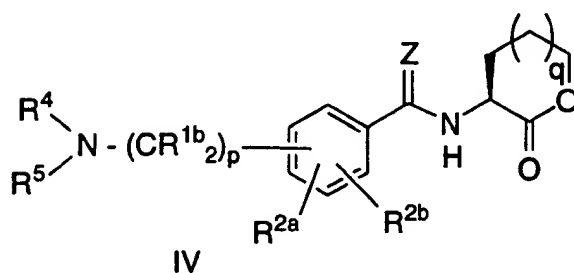
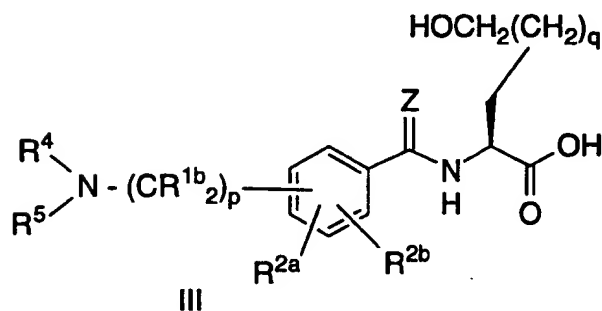
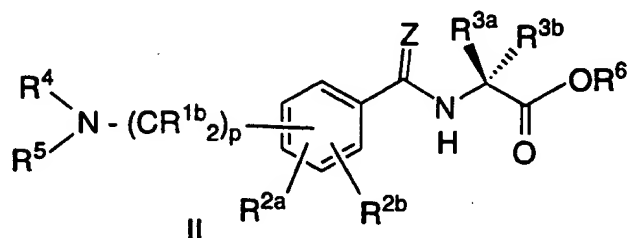
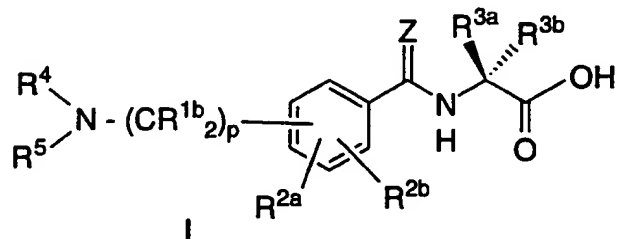
5

Z is independently H_2 or O;

- | | | |
|----|------|--|
| | m is | 0, 1 or 2; |
| | n is | 0, 1, 2, 3 or 4; |
| 10 | p is | 0, 1, 2, 3 or 4; |
| | q is | 0, 1 or 2; |
| | r is | 0 to 5, provided that r is 0 when V is hydrogen; |
| | s is | 4 or 5; |
| | t is | 3, 4 or 5; and |
| 15 | u is | 0 or 1; |

- 70 -

w) U.S. Serial Nos. 08/413,137 and 08/412,830, incorporated herein by reference,



wherein:

- 5 R^{1a} and R^{1b} are independently selected from:
- a) hydrogen,
 - b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 10

- 71 -

- 5 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R^{2a} and R^{2b} are independently selected from:

- 10 a) hydrogen,
 b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 15 c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

20

R^{3a} and R^{3b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 25 i) methionine sulfoxide, or
 ii) methionine sulfone, and
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 30 wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and

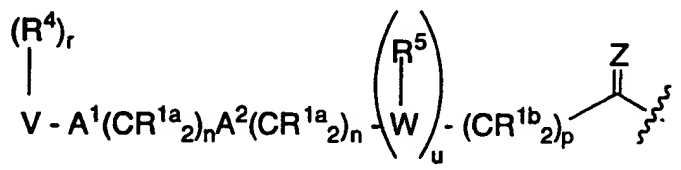
- 72 -

- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

- 5 R^{3a} and R^{3b} are combined to form - (CH₂)_s - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

R⁴ and R⁵ are independently selected from:

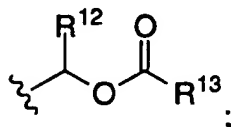
- 10 a) hydrogen, and
b)



R⁶ is

- 15 a) substituted or unsubstituted C₁-C₈ alkyl or substituted or unsubstituted C₅-C₈ cycloalkyl, wherein the substituent on the alkyl is selected from:
- 20 1) aryl,
2) heterocycle,
3) -N(R¹¹)₂,
4) -OR¹⁰, or

b)



- 25 R⁷ is independently selected from:

- a) hydrogen,
b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 30

- 73 -

- 5 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R⁸ is selected from:

- 10 a) hydrogen,
b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
15 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

20

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

R¹² is independently selected from hydrogen and C₁-C₆ alkyl;

25 R¹³ is independently selected from C₁-C₆ alkyl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

30

V is selected from:

- a) hydrogen,
b) heterocycle,
c) aryl,

- 74 -

- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl,
- provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if
- 5 A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle;

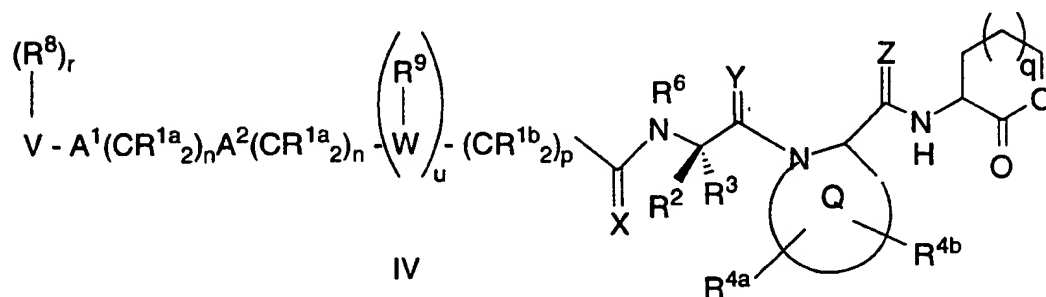
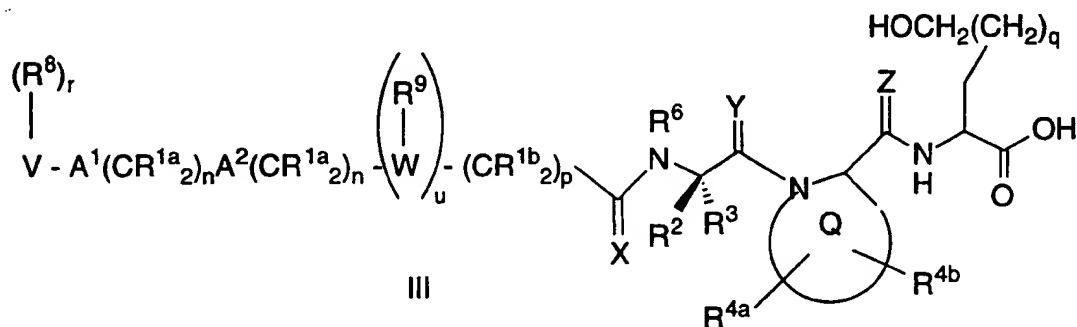
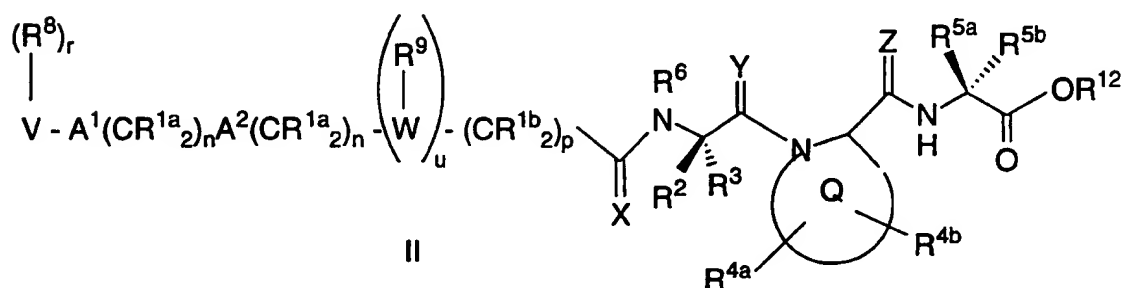
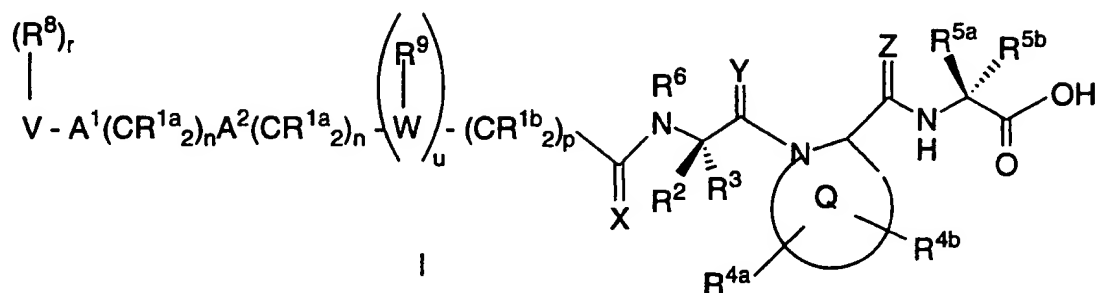
Z is independently H₂ or O;

10

- m is 0, 1 or 2;
- n is 0, 1, 2, 3 or 4;
- p is 0, 1, 2, 3 or 4;
- q is 0, 1 or 2;
- 15 r is 0 to 5, provided that r is 0 when V is hydrogen;
- s is 4 or 5; and
- u is 0 or 1;

- 75 -

x) U.S. Serial Nos. 08/412,626 and 08/412,828, incorporated herein by reference,



5 wherein:

R¹ᵃ and R¹ᵇ are independently selected from:

- 76 -

- 5
- a) hydrogen,
 - b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
 - c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;
- 10

R^2 and R^3 are independently selected from:

- 15
- a) a side chain of a naturally occurring amino acid,
 - b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone, and
 - c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclic group,

20

wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1-C_{20} alkyl, and
 - d) C_1-C_6 alkyl substituted with an unsubstituted or

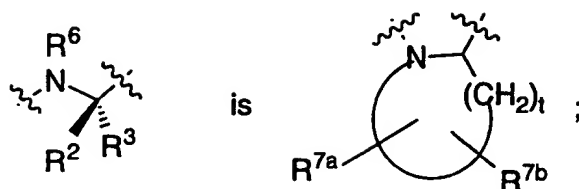
25

substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form $-(CH_2)_s-$; or

30 R^2 or R^3 are combined with R^6 to form a ring such that

- 77 -



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- 5 b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 10 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

15

R^{5a} and R^{5b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - 20 i) methionine sulfoxide, or
 - ii) methionine sulfone,
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,

wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
- 25 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or
- 30

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R5a and R5b are combined to form $-(CH_2)_s-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)-;

5 R6 is independently selected from hydrogen or C₁-C₆ alkyl;

R8 is independently selected from:

- a) hydrogen,
- 10 b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 15 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R9 is selected from:

- 20 a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 25 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

30 R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

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R¹² is

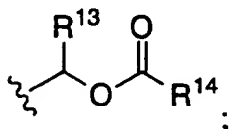
a) substituted or unsubstituted C₁-C₈ alkyl or substituted or unsubstituted C₅-C₈ cycloalkyl, wherein the substituent on the alkyl or cycloalkyl is selected from:

5

- 1) aryl,
- 2) heterocycle,
- 3) -N(R¹¹)₂,
- 4) -OR¹⁰, or

b)

10



R¹³ is independently selected from hydrogen and C₁-C₆ alkyl;

R¹⁴ is independently selected from C₁-C₆ alkyl;

15

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

20 Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C₅-C₇ saturated ring or a heterocycle;

V is selected from:

25

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- 30 e) C₂-C₂₀ alkenyl,

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

- 80 -

W is a heterocycle;

X, Y and Z are independently H₂ or O;

5

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

q is 0, 1 or 2;

10 r is 0 to 5, provided that r is 0 when V is hydrogen;

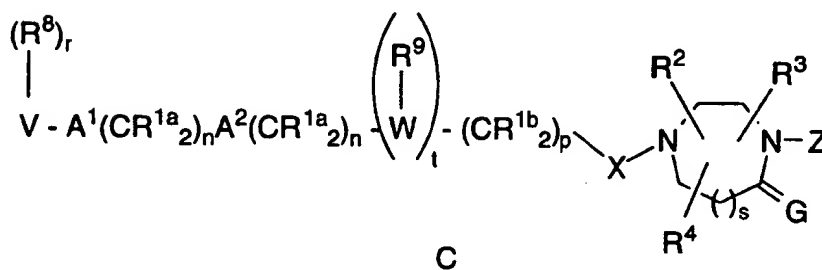
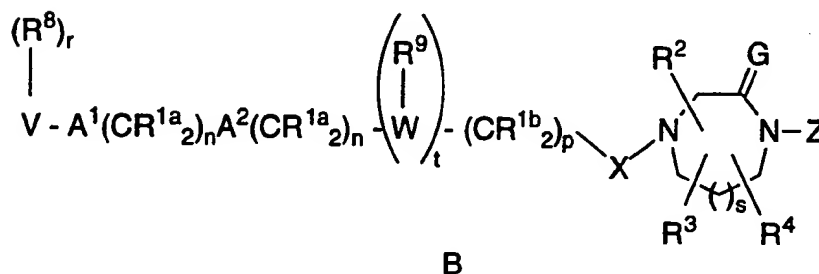
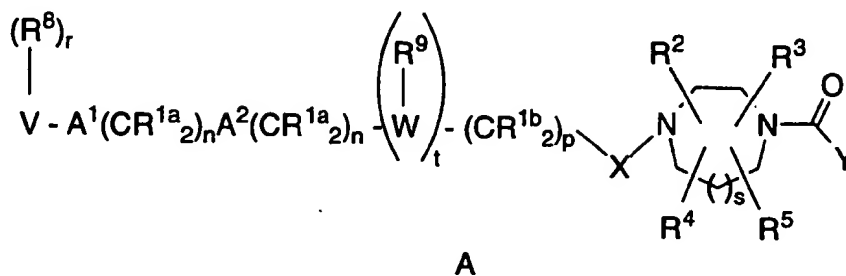
s is 4 or 5;

t is 3, 4 or 5; and

u is 0 or 1;

- 81 -

y) U.S. Serial Nos. 08/412,829 and 08/470,690, incorporated herein by reference,



wherein:

5

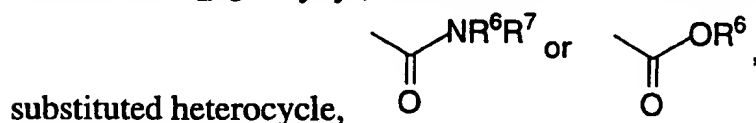
R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
 - b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 - c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆
- 10

- 82 -

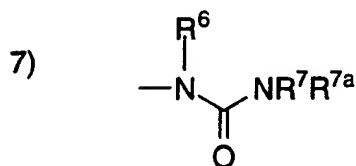
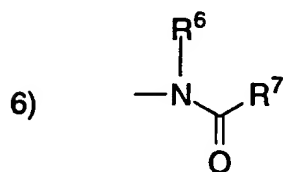
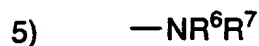
alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN,
 $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$,
 or $R^{11}OC(O)-NR^{10}-$;

- 5 R^2 and R^3 are independently selected from: H; unsubstituted or substituted C1-8 alkyl, unsubstituted or substituted C2-8 alkenyl, unsubstituted or substituted C2-8 alkynyl, unsubstituted or substituted aryl, unsubstituted or

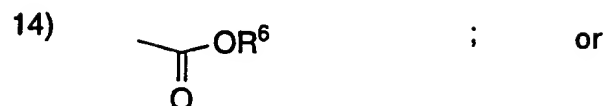
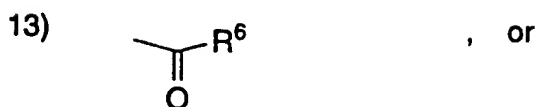
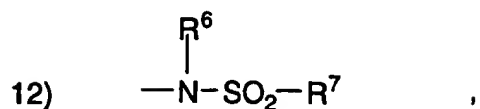
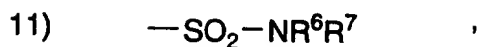
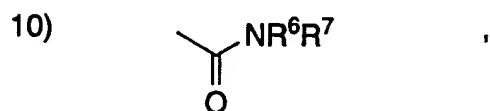
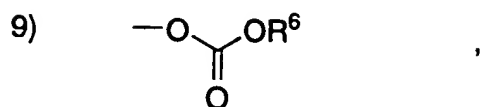
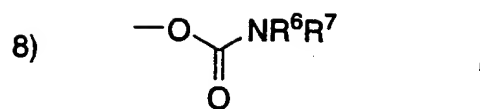


wherein the substituted group is substituted with one or more of:

- 10 1) aryl or heterocycle, unsubstituted or substituted with:
 a) C1-4 alkyl,
 b) $(CH_2)_pOR^6$,
 c) $(CH_2)_pNR^6R^7$,
 d) halogen,
 15 2) C3-6 cycloalkyl,
 3) OR^6 ,
 4) SR^6 , $S(O)R^6$, SO_2R^6 ,



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5 R^2 and R^3 are attached to the same C atom and are combined to form $(\text{CH}_2)_u$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m , —NC(O)— , and $\text{—N(COR}^{10})\text{—}$;

R^4 is selected from H and CH_3 ;

10

and any two of R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

15 R^6 , R^7 and R^{7a} are independently selected from: H; C₁-4 alkyl, C₃-6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

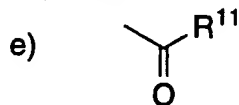
a) C₁-4 alkoxy,

- 84 -

b) aryl or heterocycle,

c) halogen,

d) HO,

f) $-\text{SO}_2\text{R}^{11}$, or5 g) $\text{N}(\text{R}^{10})_2$; or R^6 and R^7 may be joined in a ring; R^7 and R^{7a} may be joined in a ring;10 R^8 is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, CN, NO₂, $\text{R}^{10}_2\text{N}-\text{C}(\text{NR}^{10})-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$, and
- 15 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NH}-$, CN, $\text{H}_2\text{N}-\text{C}(\text{NH})-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, N_3 , $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{10}\text{OC}(\text{O})\text{NH}-$;
- 20

 R^9 is selected from:

- a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, CN, NO₂, $(\text{R}^{10})_2\text{N}-\text{C}(\text{NR}^{10})-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$, and
- 25 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, CN, $(\text{R}^{10})_2\text{N}-\text{C}(\text{NR}^{10})-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$;
- 30

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R^{10} is independently selected from hydrogen, C_1 - C_6 alkyl, benzyl and aryl;

5 R^{11} is independently selected from C_1 - C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{10}-$, $-\text{NR}^{10}\text{C}(\text{O})-$, O , $-\text{N}(\text{R}^{10})-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{10})-$, $-\text{N}(\text{R}^{10})\text{S}(\text{O})_2-$, or $\text{S}(\text{O})_m$;

10

G is H_2 or O;

V is selected from:

- 15
- a) hydrogen,
 - b) heterocycle,
 - c) aryl,
 - d) C_1 - C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
 - e) C_2 - C_{20} alkenyl,

20 provided that V is not hydrogen if A^1 is $\text{S}(\text{O})_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $\text{S}(\text{O})_m$;

W is a heterocycle;

25 X is $-\text{CH}_2-$, $-\text{C}(=\text{O})-$, or $-\text{S}(=\text{O})_m-$;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

- 30
- 1) C_1 -4 alkyl, unsubstituted or substituted with:
 - a) C_1 -4 alkoxy,
 - b) NR^6R^7 ,
 - c) C_3 -6 cycloalkyl,
 - d) aryl or heterocycle,
 - e) HO,

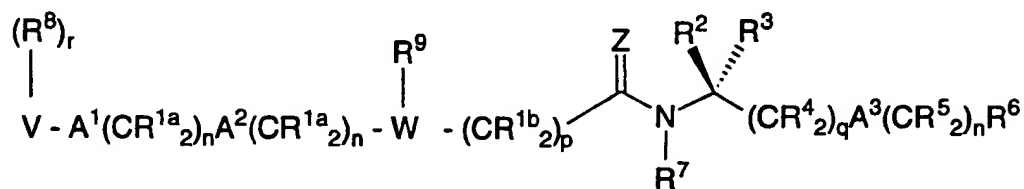
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- 20
- 25
- 30
- f) $-S(O)_mR^6$, or
g) $-C(O)NR^6R^7$,
- 2) aryl or heterocycle,
3) halogen,
4) OR^6 ,
5) NR^6R^7 ,
6) CN,
7) NO_2 ,
8) CF_3 ;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C₃-C₆ cycloalkyl;
- Z is
- aryl, heteroaryl, arylmethyl, heteroarylmethyl,
arylsulfonyl, heteroarylsulfonyl, unsubstituted or
substituted with one or more of the following:
- 1) C₁-4 alkyl, unsubstituted or substituted with:
a) C₁-4 alkoxy,
b) NR^6R^7 ,
c) C₃-6 cycloalkyl,
d) aryl or heterocycle,
e) HO,
f) $-S(O)_mR^6$, or
g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6 ,
5) NR^6R^7 ,
6) CN,
7) NO_2 ,
8) CF_3 ;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C₃-C₆ cycloalkyl;

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- m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 p is 0, 1, 2, 3 or 4;
 5 r is 0 to 5, provided that r is 0 when V is hydrogen;
 s is 0 or 1;
 t is 0 or 1; and
 u is 4 or 5;

- 10 z) U.S. Serial No. 08/468,160, incorporated herein by reference,



I

wherein:

R^{1a} is independently selected from:

- a) hydrogen,
 15 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 20 heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)-NR¹⁰-;

- 25 R^{1b} is independently selected from:

- a) hydrogen,
 b) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, C₂-C₂₀

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alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, CN, NO_2 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 or $-N(R^{10})_2$,

- c) C_1-C_6 alkyl unsubstituted or substituted by substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 or $-N(R^{10})_2$;

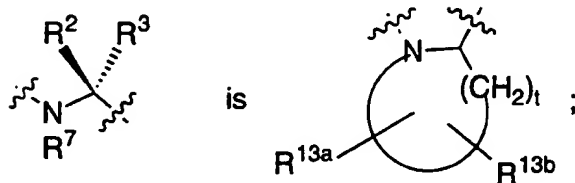
R^2 and R^3 are independently selected from:

- 10 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone, and
 15 c) substituted or unsubstituted C_1-C_{20} alkyl, substituted or unsubstituted C_2-C_{20} alkenyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 20 $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$,
 CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 ,
 $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1-C_{20} alkyl, and
 d) C_1-C_6 alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and C_3-
 25 C_{10} cycloalkyl; or

R^2 and R^3 are combined to form $-(CH_2)_s-$; or

R^2 or R^3 are combined with R^7 to form a ring such that

30



R₄, R₅, R_{13a} and R_{13b} are independently selected from:

- a) hydrogen,
- 5 b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₂₀ alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 10 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;
- 15

R₆ is selected from:

- a) hydrogen,
- 20 b) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₁-C₂₀ perfluoroalkyl, allyloxy, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, (R¹²)₂NC(O)- or R¹¹OC(O)NR¹⁰-, and
- 25 c) C₁-C₆ alkyl unsubstituted or substituted by substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₂-C₂₀ perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;
- 30

R₇ is independently selected from

- a) hydrogen,
- b) unsubstituted or substituted aryl,

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- 5 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted C₃-C₁₀ cycloalkyl, and
 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or
 substituted group selected from aryl, heterocycle and C₃-
 C₁₀ cycloalkyl;

R⁸ is selected from:

- 10 a) hydrogen,
 b) substituted or unsubstituted aryl, substituted or unsubstituted
 heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, C₂-C₂₀
 alkynyl, C₁-C₂₀ perfluoroalkyl, allyloxy, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, -S(O)₂NR¹⁰₂, CN, NO₂,
 R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂,
 or R¹¹OC(O)NR¹⁰-, and
 15 c) C₁-C₆ alkyl unsubstituted or substituted by substituted or
 unsubstituted aryl, substituted or unsubstituted heterocycle,
 C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₂-
 C₂₀ perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
 R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-,
 20 N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R⁹ is selected from:

- 25 a) hydrogen,
 b) C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₂-C₂₀ perfluoroalkyl, F,
 Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 c) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₂₀
 perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
 30 R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-,
 R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and
 aryl;

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R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

5 R¹² is independently selected from hydrogen, C₁-C₆ alkyl and aryl, or
(R¹²)₂ forms - (CH₂)_s - ;

A¹, A² and A³ are independently selected from: a bond, -CH=CH-,
-C≡C-, -C(O)-, -C(O)NR⁷-, -NR⁷C(O)-, O, -N(R⁷)-,
-S(O)₂N(R⁷)-, -N(R⁷)S(O)₂-, or S(O)_m;

10

V is selected from:

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- 15 d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced
with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl,

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if
A¹ is a bond, n is 0 and A² is S(O)_m;

20

W is a heterocycle;

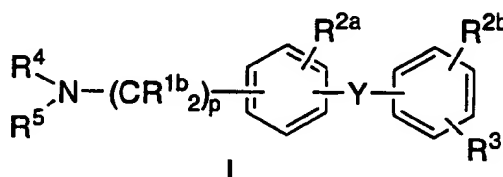
Z is independently H₂ or O;

- 25 m is 0, 1 or 2;
- n is 0, 1, 2, 3 or 4;
- p is 0, 1, 2, 3 or 4;
- q is 0, 1, 2, 3 or 4;
- r is 0 to 5, provided that r is 0 when V is hydrogen;
- 30 s is 4 or 5; and
- t is 3, 4 or 5;

and

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aa) U.S. Serial No. 08/449,038, incorporated herein by reference,



wherein:

5

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-,
- c) C₁-C₆ alkyl unsubstituted or substituted by unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)-NR⁸-;

20 R^{2a}, R^{2b} and R³ are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, N₃, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-,
- c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted cycloalkyl, alkenyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, halogen or R⁹OC(O)NR⁸-, and

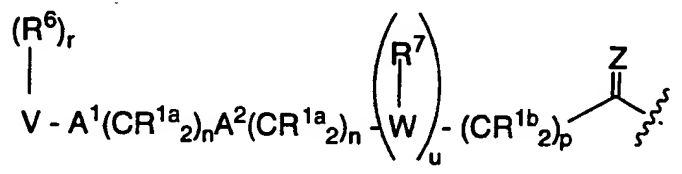
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- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

5 R⁴ and R⁵ are independently selected from:

- a) hydrogen, and
b)



10 R⁶ is independently selected from:

- a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, R⁸₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and

15

- c) C₁-C₆ alkyl unsubstituted or substituted by unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NH-, CN, H₂N-C(NH)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁸OC(O)NH-;

20

25 R⁷ is selected from:

- a) hydrogen,
b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-,

30

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CN, $(R^8)_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3 , $-N(R^8)_2$,
or $R^9OC(O)NR^8-$;

5 R^8 is independently selected from hydrogen, C₁-C₆ alkyl, substituted or
unsubstituted C₁-C₆ aralkyl and substituted or unsubstituted
aryl;

R^9 is independently selected from C₁-C₆ alkyl and aryl;

10 R^{10} is independently selected from hydrogen, C₁-C₆ alkyl, substituted or
unsubstituted C₁-C₆ aralkyl and substituted or unsubstituted
aryl;

15 A^1 and A^2 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$,
 $-C(O)-$, $-C(O)NR^8-$, $-NR^8C(O)-$, O, $-N(R^8)-$, $-S(O)_2N(R^8)-$,
 $-N(R^8)S(O)_2-$, or $S(O)_m$;

V is selected from:

- 20 a) hydrogen,
b) heterocycle,
c) aryl,
d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced
with a heteroatom selected from O, S, and N, and
e) C₂-C₂₀ alkenyl,

25 provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if
 A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

30 Y is selected from: a bond, $-C(R^{10})=C(R^{10})-$, $-C\equiv C-$, $-C(O)-$, $-C(R^{10})_2-$,
 $-C(OR^{10})R^{10}-$, $-CN(R^{10})_2R^{10}-$, $-OC(R^{10})_2-$, $-NR^{10}C(R^{10})_2-$,
 $-C(R^{10})_2O-$, $-C(R^{10})_2NR^{10}-$, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, O,
 $-NC(O)R^{10}-$, $-NC(O)OR^{10}-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$, or
 $S(O)_m$;

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Z is H₂ or O;

- m is 0, 1 or 2;
5 n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
u is 0 or 1;

- 10 or the pharmaceutically acceptable salts thereof.

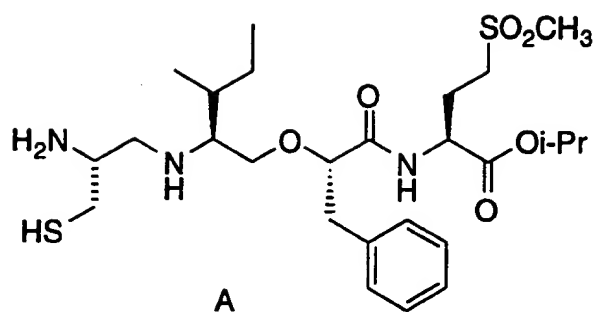
The composition of the instant invention may alternatively or in addition comprise a protein substrate-competitive inhibitor obtained by fermentation of cultures of novel organisms. In particular, the
15 compounds disclosed in the following patents and publications may be useful as a protein substrate-competitive inhibitor component of the instant composition: U.S. Pat. No. 5,420,334; and 08/435,047. Those patents and publications are incorporated herein by reference.

In addition, compounds described in the following patents
20 and publications may also be utilized as a protein substrate-competitive inhibitor component of the instant composition: U.S. Pat. No. 5,420,245; European Pat. Publ. 0 618 221; PCT Pat. Publs. WO 94/26723; WO 95/10514; WO 95/10515; WO 95/10516; WO 95/08542; WO 95/11917; and WO 95/12612. Those patents and publications are incorporated
25 herein by reference.

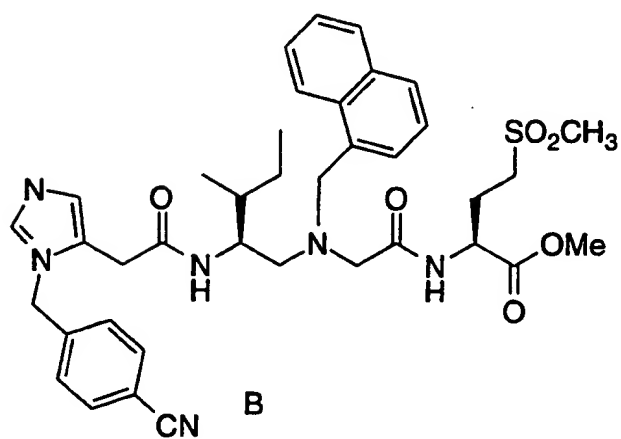
Specific examples of protein substrate-competitive inhibitors useful in the compositions of the invention are:

Compound A:

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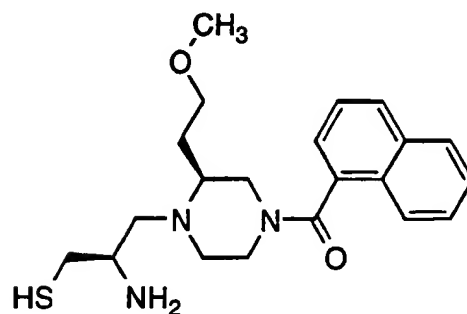


Compound B:



5

and Compound E:



10 or the pharmaceutically acceptable salts thereof.

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Other specific examples of protein substrate-competitive inhibitors useful in the compositions of the invention are:

- 5 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-n-propyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-methyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 10 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-ethyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-i-propyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 15 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-n-butyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 20 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-s-butyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-t-butyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 25 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-cyclohexyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 30 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-cyclopentyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,

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- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-benzyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6-methyl-2(R)-i-propyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-i-propyl-3,4-E-octenoyl-methionine, and the corresponding methyl ester,
- 10 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-n-butyl-3,4-E-octenoyl-methionine, and the corresponding methyl ester,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-benzyl-3,4-E-octenoyl-methionine, and the corresponding methyl ester,
- 15 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-n-propyl-octanoyl-homoserine, and the corresponding homoserine lactone,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-benzyl-octanoyl-homoserine, and the corresponding homoserine lactone,
- 20 N-(3-phenyl-2(S)-(mercaptopropionylamino)prop-1-yl)isoleucyl-methionine,
- 25 N-(2(R)-amino-3-mercaptopropyl)isoleucyl-phenylalanyl-methionine,
- N-(3-mercaptopropyl)isoleucyl-phenylalanyl-methionine,
- N-(3-mercaptopropyl)valyl-isoleucyl-methionine,
- 30 N-(2(R)-amino-3-mercaptopropyl)valyl-isoleucyl-methionine,
- N-(3-methyl-2(S)-(cysteinyllamino)but-1-yl)phenylalanyl-methionine,

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N-(3-methyl-2(S)-(mercaptopropionylamino)but-1-yl)-phenylalanyl-methionine,

5 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)methylpentyl]-phenylalanyl-methionine,

N-[2(S)-(3-mercaptopropylamino)-3(S)methylpentyl]-phenylalanyl-methionine,

10 N-(2(R)-amino-3-mercaptopropyl)isoleucyl-phenylalanyl-(methionine sulfone),

N-(2(R)-amino-3-mercaptopropyl)isoleucyl)-(p-iodophenylalanyl)-methionine,

15 N-[2(R)-(cysteinyl-isoleucylamino)-3(S)-methylpentyl]-methionine,

N-[2(R)-(N'-(2(R)-amino-3-mercaptopropyl)-isoleucylamino)-3-phenylpropyl]methionine,

20 N-[2(R)-(N'-(2(R)-amino-3-mercaptopropyl)-isoleucylamino)-3(S)-methylpentyl]methionine,

25 N-(3-mercaptopropyl)valyl-isoleucyl-methionine methyl ester,

N-(2(R)-amino-3-mercaptopropyl)isoleucyl-phenylalanyl-methionine ethyl ester,

30 N-(2(R)-amino-3-mercaptopropyl)isoleucyl-phenylalanyl-methionine benzyl ester,

N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-phenethylamide,

N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-benzylamide,

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- N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-3-methylbutylamide,
- N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-3-phenylpropylamide,
- 5 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucyl-L-phenylalaninol,
- N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-N'-methylbenzylamide,
- 10 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(4-methoxybenzyl)amide,
- N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2,4-dichloro-benzyl)amide,
- 15 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(4-trifluoromethyl-benzyl)amide,
- N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2,4-dichloro-phenethyl)amide,
- 20 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2-benzimidazol-ylmethyl)amide,
- 25 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(1-indanyl)amide,
- N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2,4-dimethyl-benzyl)amide,
- 30 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2,3-dichloro-benzyl)amide,
- N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(4-sulfamoyl-benzyl)amide,

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- N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucineanilide,
- 5 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2,4-dimethyl-phenyl)amide,
- N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2,3-dimethyl-phenyl)amide,
- 10 L-Cysteinyl-L-isoleucine-phenethylamide,
- N-[2(S)-[2(R)-Amino-3-mercaptopropylamino]-3-methylpentyl]-phenethylamide,
- 15 N-(2(R)-Amino-3-mercaptopropyl)-L-alaninebenzylamide,
- N-Benzyl-[2(S)-2(R)-Amino-3-mercaptopropyl)-amino]butyramide,
- N-(2(R)-Amino-3-mercaptopropyl)-L-norleucinebenzylamide,
- 20 N-(2(R)-Amino-3-mercaptopropyl)-L-norvalinebenzylamide,
- N-(2(R)-Amino-3-mercaptopropyl)isoleucyl-phenylalanyl-homoserine,
- 25 N-(2(R)-Amino-3-mercaptopropyl)isoleucyl-isoleucyl-homoserine,
- N-(2(R)-Amino-3-mercaptopropyl)isoleucyl-phenylalanyl-homoserine lactone,
- 30 N-(2(R)-Amino-3-mercaptopropyl)isoleucyl-isoleucyl-homoserine lactone,
- N-(2(R)-Amino-3-mercaptopropyl)isoleucyl-phenylalanyl-homocysteine lactone,

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- N-[2(S)-(2(R)-Amino-3-mercaptopropyl)-3(S)-methylpentyl]-isoleucyl-homoserine lactone,
- 5 N-[N'-(2(R)-Amino-3-mercaptopropyl)isoleucyl-phenylalanyl]-3(S)-amino-tetrahydropyran-2-one,
- N-[N'-(2(R)-Amino-3-mercaptopropyl)isoleucyl-isoleucyl]-3(S)-amino-tetrahydropyran-2-one,
- 10 N-(2(R)-Amino-3-mercaptopropyl)isoleucyl-isoleucyl-homocysteine lactone,
- N-[2(S)-(2(R)-Amino-3-mercaptopropylamino)-3(S)-methyl
- 15 pentyl]isoleucyl-homoserine,
- N-[N'-(2(R)-Amino-3-mercaptopropyl)isoleucyl-phenylalanyl]-3(S)-amino-4-hydroxypentanoic acid,
- 20 N-[N'-(2(R)-Amino-3-mercaptopropyl)isoleucyl-isoleucyl]-3(S)-amino-4-hydroxypentanoic acid,
- N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucyl-homoserine,
- 25 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucyl-homoserine lactone,
- N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-
- 30 methyl-phenylalanyl-homoserine,
- N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-phenylalanyl-homoserine lactone,

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N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3-methyl-butyl]-N-methyl-phenylalanyl-homoserine,

5 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3-methyl-butyl]-N-methyl-phenylalanyl-homoserine lactone,

3(S)-{N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methyl-pentyl]-N-methyl-isoleucylamino}-3-methyltetra-hydropyran-2-one,

10 2(S)-{N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methyl-pentyl]-N-methyl-isoleucylamino}-2-methyl-5-hydroxypentanoic acid,

2(S)-{N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucylamino}-5-methyl-5-hydroxyhexanoic acid,

15 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-norvalyl-homoserine,

20 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-norvalyl-homoserine lactone,

N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucyl-methionine,

25 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucyl-methionine methyl ester,

N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-phenylalanyl-methionine,

30 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-phenylalanyl-methionine methyl ester,

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3(S)-{N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methyl-
pentyl]-N-methyl-isoleucylamino}-6,6-dimethyl-tetrahydropyran-2-one,

5 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-
methyl-norvalyl-methionine,

N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-
methyl-norvalyl-methionine methyl ester,

10 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-
methyl-D-norvalyl-homoserine,

N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-
methyl-D-norvalyl-homoserine lactone,

15 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-homoserine lactone,

20 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-2-methyl-3-phenylpropionyl-homoserine lactone,

25 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-4-pentenoyl-homoserine lactone,

30 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-4-pentenoyl-homoserine,

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- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxypentanoyl-homoserine lactone,
- 5 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxypentanoyl-homoserine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-4-methylpentanoyl-homoserine lactone,
- 10 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-4-methylpentanoyl-homoserine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-methylbutanoyl-homoserine lactone,
- 15 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-methylbutanoyl-homoserine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
20 pentyloxy-3-phenylbutanoyl-homoserine lactone,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylbutanoyl-homoserine,
- 25 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentylothio-2-methyl-3-phenylpropionyl-homoserine lactone,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentylothio-2-methyl-3-phenylpropionyl-homoserine,
- 30 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine lactone,

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- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine,
- 5 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-methionine methyl ester,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-methionine,
- 10 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-methionine sulfone,
- 15 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-naphth-2-yl-propionyl-methionine sulfone methyl ester,
- 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
20 pentyloxy-3-naphth-2-yl-propionyl-methionine sulfone,
- 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone methyl ester,
- 25 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone,
- 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-methybutanoyl-methionine methyl ester,
- 30 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-methybutanoyl-methionine,

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- Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone,
- 5 Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine,
- Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methylbutanoyl-methionine methyl ester.
- 10 1-[2-(R)-Amino-3-mercaptopropyl]-2(S)-(1-butyl)-4-(2,3-dimethylbenzoyl)piperazine dihydrochloride
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(n-butyl)-4-(1-naphthoyl)piperazine
- 15 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-benzyl-4-[1-(2,3-dimethyl)benzoyl]piperazine
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(2-methoxy)ethyl-4-[1-(2,3-dimethyl)benzoyl]piperazine
- 20 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(2-methylthio)ethyl-4-[1-(2,3-dimethyl)benzoyl]piperazine
- 25 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(n-butyl)-4-[7-(2,3-dihydrobenzofuroyl)]piperazine
- 1-(2(R)-Amino-3-mercaptopropyl)-4-(1-naphthoyl)-2(S)-pyridinylcarboxyl-4-piperazine dihydrochloride
- 30 Methyl 4-(2(R)-amino-3-mercaptopropyl)-1-(1-naphthylmethyl)piperazine-2-carboxylate hydrochloride
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(2-methoxyethyl)-4-(1-naphthoyl)piperazine
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- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-*n*-butyl-4-(8-quinolinylcarbonyl)piperazine
- 5 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(2-(1-propoxy)ethyl)-4-(1-naphthoyl)piperazine
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(3-methoxy-1-propyl)-4-(1-naphthoyl)piperazine
- 10 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(2-(1-propoxy)ethyl)-4-(8-quinolinoyl)piperazine
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-[(3-pyridyl)methoxyethyl]-4-(1-naphthoyl)piperazine
- 15 1-[2(R)-Amino-3-mercaptopropyl]-4-naphthoyl-2(S)-(2-phenylsulfonyl-ethyl)piperazine dihydrochloride
- 20 *bis*-1,1'-[2(R)-Amino-3-(2(S)-(2-methoxyethyl)-4-naphthoyl-1-piperazinyl)]propyl disulfide tetrahydrochloride
- bis*-1,1'-[2(R)-Amino-3-(4-naphthoyl-2(S)-(2-phenylsulfonyl-ethyl)-1-piperazinyl)]propyl disulfide tetrahydrochloride
- 25 1-[2(R)-Amino-3-mercaptopropyl]-4-naphthoyl-2(S)-(2-cyclopropyloxyethyl)piperazine dihydrochloride
- 1-[2(R)-Amino-3-mercaptopropyl]-4-(1-naphthoyl)-2(S)-(4-acetamidobutyl)piperazine dihydrochloride
- 30 1-[2(R)-Amino-3-mercaptopropyl]-4-naphthoyl-2(S)-(2-cyclopropylmethylsulfonyl-ethyl)piperazine dihydrochloride
- 35 Pyroglutamyl-valyl-phenylalanyl-methionine

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- Pyroglutamyl-valyl-phenylalanyl-methionine methyl ester;
- Pyroglutamyl-valyl-isoleucyl-methionine;
- 5 Pyroglutamyl-valyl-isoleucyl-methionine methyl ester;
- Nicotinoyl-isoleucyl-phenylalanyl-methionine;
- 10 Nicotinoyl-isoleucyl-phenylalanyl-methionine methyl ester;
- N-[2(S)-(L-Pyroglutamylamino)-3-methylbutyl]phenylalanyl-methionine;
- N-[2(S)-(L-Pyroglutamylamino)-3-methylbutyl]phenylalanyl-methionine
- 15 methyl ester;
- N-[5(S)-(L-Pyroglutamylamino)-6(S)-methyl-2(R)-butyl-3,4(E)-octenoyl]-methionine;
- 20 N-[5(S)-(L-Pyroglutamylamino)-6(S)-methyl-2(R)-butyl-3,4(E)-octenoyl]-methionine methyl ester;
- N-[5(S)-((Imidazol-4-yl)acetylamino)-6(S)-methyl-2(R)-butyl-3,4(E)-octenoyl]-methionine;
- 25 N-[5(S)-((Imidazol-4-yl)acetylamino)-6(S)-methyl-2(R)-butyl-3,4(E)-octenoyl]-methionine methyl ester;
- N-[5(S)-((Imidazol-4-ylcarbonylamino)-6(S)-methyl-2(R)-butyl-3,4(E)-octenoyl]-methionine;
- 30 N-[5(S)-((Imidazol-4-ylcarbonylamino)-6(S)-methyl-2(R)-butyl-3,4(E)-octenoyl]-methionine methyl ester;

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N-[2(S)-(2(S)-(Imidazol-4-yl)acetyl-amino)-3(S)-methylpent-yloxy)-3-phenylpropionyl]-methionine;

5 N-[2(S)-(2(S)-(Imidazol-4-yl)acetyl-amino)-3(S)-methylpent-yloxy)-3-phenylpropionyl]-methionine methyl ester;

N-[2(S)-(2(S)-Pyroglutamyl-amino)-3(S)-methylpent-yloxy)-3-phenylpropionyl]-methionine;

10 N-[2(S)-(2(S)-Pyroglutamyl-amino)-3(S)-methylpent-yloxy)-3-phenylpropionyl]-methionine methyl ester;

N-[2(S)-(2(S)-Imidazol-4-ylcarbonyl)-amino)-3(S)-methylpent-yloxy)-3-phenylpropionyl]-methionine;

15 N-[2(S)-(2(S)-Imidazol-4-ylcarbonyl)-amino)-3(S)-methylpent-yloxy)-3-phenylpropionyl]-methionine methyl ester;

20 N-[2(S)-(2(S)-((3-Picolinyl)-amino)-3(S)-methylpent-yloxy)-3-phenylpropionyl]-methionine;

N-[2(S)-(2(S)-((3-Picolinyl)-amino)-3(S)-methylpent-yloxy)-3-phenylpropionyl]-methionine methyl ester;

25 N-[2(S)-(2(S)-((Histidyl)-amino)-3(S)-methylpent-yloxy)-3-phenylpropionyl]-methionine;

N-[2(S)-(2(S)-((Histidyl)-amino)-3(S)-methylpent-yloxy)-3-phenylpropionyl]-methionine methyl ester;

30 N-Benzyl-N-[2(S)-((Imidazol-4-ylcarbonyl)-amino)-3(S)-methylpentyl]-glycyl-methionine;

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N-Benzyl-N-[2(S)-((Imidazol-4-ylcarbonyl)amino)-3(S)-methylpentyl]-glycyl-methionine methyl ester;

5 N-Benzyl-N-[2(S)-((Imidazol-4-ylacetyl)amino)-3(S)-methylpentyl]-glycyl-methionine;

N-Benzyl-N-[2(S)-((Imidazol-4-ylacetyl)amino)-3(S)-methylpentyl]-glycyl-methionine methyl ester;

10 N-Benzyl-N-[2(S)-((Pyroglutamyl)amino)-3(S)-methylpentyl]-glycyl-methionine;

N-Benzyl-N-[2(S)-((Pyroglutamyl)amino)-3(S)-methylpentyl]-glycyl-methionine methyl ester;

15

N-(1-Naphthylmethyl)-N-[2(S)-((imidazol-4-ylcarbonyl)amino)-3(S)-methylpentyl]-glycyl-methionine;

20 N-(1-Naphthylmethyl)-N-[2(S)-((imidazol-4-ylcarbonyl)amino)-3(S)-methylpentyl]-glycyl-methionine methyl ester;

N-(1-Naphthylmethyl)-N-[2(S)-((imidazol-4-ylacetyl)amino)-3(S)-methylpentyl]-glycyl-methionine;

25 N-(1-Naphthylmethyl)-N-[2(S)-((imidazol-4-ylacetyl)amino)-3(S)-methylpentyl]-glycyl-methionine methyl ester;

N-(1-Naphthylmethyl)-N-[2(S)-((pyroglutamyl)amino-3(S)-methylpentyl)-glycyl-methionine; and

30

N-(1-Naphthylmethyl)-N-[2(S)-((pyroglutamyl)amino-3(S)-methylpentyl)-glycyl-methionine methyl ester;

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N-[1-(Pyroglutamylamino)cyclopent-1-ylmethyl]-N-(1-naphthylmethyl)-glycyl-methionine methyl ester

5 N-[1-(Pyroglutamylamino)-cyclopent-1-ylmethyl]-N-(1-naphthylmethyl)-glycyl-methionine

N-(2(S)-L-Histidylamino-3(S)-methylpentyl)-N-(benzylmethyl)glycyl-methionine methyl ester

10 N-(2(S)-L-Histidylamino-3(S)-methylpentyl)-N-(benzylmethyl)glycyl-methionine

N-(2(S)-L-Histidylamino-3(S)-methylpentyl)-N-(1-naphthylmethyl)-glycyl-methionine methyl ester

15 N-(2(S)-L-Histidylamino-3(S)-methylpentyl)-N-(1-naphthylmethyl)-glycyl-methionine

20 2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-methylbutanoyl-methionine methyl ester

2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-methylbutanoyl-methionine

25 2(S)-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyloxy]-3-methylbutanoyl-methionine methyl ester

2(S)-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyloxy]-3-methylbutanoyl-methionine

30 N-(Benzyl)-N-[2(S)-(2-oxopyrrolidin-5(R,S)-ylmethyl)amino-3(S)-methylpentyl]-glycyl-methionine methyl ester

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- N-(Benzyl)-N-[2(S)-(2-oxopyrrolidin-5(R,S)-ylmethyl)amino-3(S)-methylpentyl]-glycyl-methionine
- 5 N-(Benzyl)-N-{2(S)-[[(D,L)-2-thiazolyl)alanyl]amino]-3(S)-methylpentyl}-glycyl-methionine methyl ester
- N-(Benzyl)-N-{2(S)-[[(D,L)-2-thiazolyl)alanyl]amino]-3(S)-methylpentyl}-glycyl-methionine
- 10 N-(Benzyl)-N-[2(S)-(3-pyridylmethyl)amino-3(S)-methylpentyl]-glycyl-methionine methyl ester
- N-(Benzyl)-N-[2(S)-(3-pyridylmethyl)amino-3(S)-methylpentyl]-glycyl-methionine
- 15 2(S)-[2(S)-(2-Oxopyrrolidin-5(S)-ylmethyl)amino-3(S)-methylpentyloxy]-3-phenylpropionyl-methionine methyl ester
- 20 2(S)-[2(S)-(2-Oxopyrrolidin-5(S)-ylmethyl)amino-3(S)-methylpentyloxy]-3-phenylpropionyl-methionine
- 25 2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-(1-naphthyl)propionyl-methionine sulfone methyl ester
- 30 2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-(2-naphthyl)propionyl-methionine sulfone methyl ester
- 35 2(S)-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyloxy]-3-(1-naphthyl)propionyl-methionine sulfone methyl ester

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- 2(S)-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyloxy]-3-(1-naphthyl)propionyl-methionine sulfone
- 5 2(S)-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyloxy]-3-(2-naphthyl)propionyl-methionine sulfone methyl ester
- 2(S)-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyloxy]-3-(2-naphthyl)propionyl-methionine sulfone
- 10 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(3-quinolylmethyl)glycyl-methionine methyl ester
- N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(3-quinolylmethyl)glycyl-methionine
- 15 N-(Benzyl)-N-[2(S)-(tetrazol-1-ylacetyl)amino-3(S)-methylpentyl]-glycyl-methionine methyl ester
- 20 N-(Benzyl)-N-[2(S)-(tetrazol-1-ylacetyl)amino-3(S)-methylpentyl]-glycyl-methionine
- N-(Benzyl)-N-[2(S)-nicotinoylamino-3(S)-methylpentyl]-glycyl-methionine methyl ester
- 25 N-(Benzyl)-N-[2(S)-nicotinoylamino-3(S)-methylpentyl]-glycyl-methionine
- N-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)-glycyl-methionine sulfoxide methyl ester
- 30 N-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)-glycyl-methionine sulfoxide

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2(S)-{2(S)-[2(S,R)-(Imidazol-4-yl)-2-aminoacetyl]amino}-3(S)-methylpentyloxy}-3-phenylpropionyl-methionine sulfone methyl ester

5 2(S)-{2(S)-[2(S,R)-(Imidazol-4-yl)-2-aminoacetyl]amino}-3(S)-methylpentyloxy}-3-phenylpropionyl-methionine sulfone

2(S)-{2(S)-[2(R,S)-(Imidazol-4-yl)-2-aminoacetyl]amino}-3(S)-methylpentyloxy}-3-phenylpropionyl-methionine sulfone methyl ester

10 2(S)-{2(S)-[2(R,S)-(Imidazol-4-yl)-2-aminoacetyl]amino}-3(S)-methylpentyloxy}-3-phenylpropionyl-methionine sulfone

15 N-{2(S)-[2(S,R)-(Imidazol-4-yl)-2-aminoacetyl]amino}-3(S)-methylpentyloxy}-N-(1-naphthylmethyl)-glycyl-methionine methyl ester

N-{2(S)-[2(S,R)-(Imidazol-4-yl)-2-aminoacetyl]amino}-3(S)-methylpentyloxy}-N-(1-naphthylmethyl)-glycyl-methionine

20 N-{2(S)-[2(R,S)-(Imidazol-4-yl)-2-aminoacetyl]amino}-3(S)-methylpentyloxy}-N-(1-naphthylmethyl)-glycyl-methionine methyl ester

N-{2(S)-[2(R,S)-(Imidazol-4-yl)-2-aminoacetyl]amino}-3(S)-methylpentyloxy}-N-(1-naphthylmethyl)-glycyl-methionine

25 N-{2(S)-[(Imidazol-4-yl)methyl]amino}-3(S)-methylpentyloxy}-N-(1-naphthylmethyl)-glycyl-methionine methyl ester

30 N-{2(S)-[(Imidazol-4-yl)methyl]amino}-3(S)-methylpentyloxy}-N-(1-naphthylmethyl)-glycyl-methionine

N-[2(S)-(L-pyroglutamyl)amino]-3(S)-methylpentyloxy}-N-(1-naphthylmethyl)-glycyl-methionine isopropyl ester

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N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-methionine t-butyl ester

5 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(4-quinolyl-methyl)glycyl-methionine methyl ester

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(4-quinolyl-methyl)glycyl-methionine

10 N-{2(S)-[3-(Imidazol-4-yl)propyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)glycyl-methionine methyl ester

N-{2(S)-[3-(Imidazol-4-yl)propyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)glycyl-methionine

15 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-norleucine

20 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-norleucine methyl ester

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-glutamine

25 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-glutamine t-butyl ester

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-[5-(dimethyl-amino)naphthylsulfonyl]glycyl-methionine methyl ester

30 N-[2(S)-(3-pyridylmethyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-methionine

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2(S)-{2(S)-[2-(Imidazol-4-yl)ethyl]amino-3(S)-methylpentyl}-3-phenylpropionyl-methionine sulfone methyl ester

5 2(S)-{2(S)-[2-(Imidazol-4-yl)ethyl]amino-3(S)-methylpentyl}-3-phenylpropionyl-methionine sulfone

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-serine methyl ester

10 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-(D,L)-serine

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-(L,D)-serine

15 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-homoserine lactone

20 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-homoserine

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(cinnamyl)glycyl-methionine methyl ester

25 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(cinnamyl)glycyl-methionine

N-{2(S)-[2-(Imidazol-4-yl)ethyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)glycyl-methionine methyl ester

30 N-{2(S)-[2-(Imidazol-4-yl)ethyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)glycyl-methionine

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N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-alanine methyl ester

5 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-alanine

N-[2(S)-(D-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-methionine methyl ester

10 N-[2(S)-(D-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-methionine

2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-phenyl-propionyl-methionine sulfone methyl ester

15 2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-phenyl-propionyl-methionine sulfone

20 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(2,3-methylenedioxybenzyl)glycyl-methionine methyl ester

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(2,3-methylenedioxybenzyl)glycyl-methionine

25 N-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyl]-N-(2,3-dihydrobenzofuran-7-ylmethyl)glycyl-methionine methyl ester

N-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyl]-N-(2,3-dihydrobenzofuran-7-ylmethyl)glycyl-methionine

30 N-{2(S)-[3-(3-indolyl)propionyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)glycyl-methionine methyl ester

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N-{2(S)-[3-(3-indolyl)propionyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)glycyl-methionine

5 N-{2(S)-[3-(1-indolyl)propionyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)glycyl-methionine methyl ester

N-{2(S)-[3-(1-indolyl)propionyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)glycyl-methionine

10 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-histidine methyl ester

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-histidine

15 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(cyclopropylmethyl)glycyl-methionine methyl ester

20 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(cyclopropylmethyl)glycyl-methionine

N-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyl]-N-(cyclopropylmethyl)glycyl-methionine methyl ester

25 N-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyl]-N-(cyclopropylmethyl)glycyl-methionine

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(2,3-dihydrobenzofuran-7-ylmethyl)glycyl-methionine methyl ester

30 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(2,3-dihydrobenzofuran-7-ylmethyl)glycyl-methionine

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- 2(S)-[2(S)-N-(L-Pyroglutamyl)-N-methylamino-3(S)-methylpentyl]oxy]-
3-phenylpropionyl-methionine methyl ester
- 2(S)-[2(S)-N-(L-Pyroglutamyl)-N-methylamino-3(S)-methylpentyl]oxy]-
5 3-phenylpropionyl-methionine
- N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-
naphthylmethyl)glycyl-O-methylserine methyl ester
- 10 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-
naphthylmethyl)glycyl-O-methylserine
- N-(1-Naphthylmethyl)-N-[2(S)-(N'-(L-pyroglutamyl)-N'-methylamino)-
3(S)-methylpentyl]-glycyl-methionine methyl ester
- 15 N-(1-Naphthylmethyl)-N-[2(S)-(N'-(L-pyroglutamyl)-N'-methylamino)-
3(S)-methylpentyl]-glycyl-methionine
- N-[1-(Pyroglutamylamino)cyclopent-1-ylmethyl]-N-(1-naphthylmethyl)-
20 glycyl-methionine methyl ester
- N-[1-(Pyroglutamylamino)-cyclopent-1-ylmethyl]-N-(1-naphthylmethyl)-
glycyl-methionine
- 25 N-[2(S)-(Pyridin-2-on-6-ylcarbonyl)amino-3(S)-methylpentyl]-N-(1-
naphthylmethyl)glycyl-methionine methyl ester
- N-[2(S)-(Pyridin-2-on-6-ylcarbonyl)amino-3(S)-methylpentyl]-N-(1-
naphthylmethyl)glycyl-methionine
- 30 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(3-chloro-
benzyl)glycyl-methionine methyl ester
- N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(3-chloro-
35 benzyl)glycyl-methionine

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N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-O-methylhomoserine methyl ester

- 5 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-O-methylhomoserine

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(2,3-dimethyl-benzyl)glycyl-methionine methyl ester

10

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(2,3-dimethyl-benzyl)glycyl-methionine

- 15 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-(2-thienyl)alanine methyl ester

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-(2-thienyl)alanine

- 20 N-[2(S)-(pyrrolidin-2-on-1-yl)-3-methylbutanoyl]-isoleucyl-methionine;

N-[2(S)-(piperidin-2-on-1-yl)-3-methylbutanoyl]-isoleucyl-methionine;

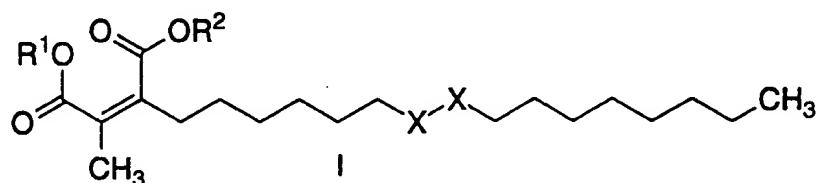
or the pharmaceutically acceptable salts or optical isomers thereof.

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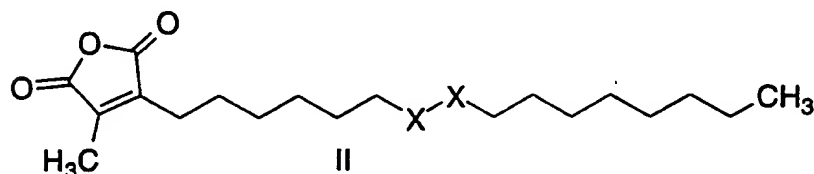
The composition of the instant invention also comprises a farnesyl pyrophosphate-competitive inhibitor. Thus the following compounds, well known in the art, are useful as farnesyl pyrophosphate-competitive inhibitors in the instant invention:

5

bb) U.S.Pat. No. 5,260,465, incorporated herein by reference,



or



wherein:

- 10 X - X is: CH = CH (cis);
CH = CH (trans); or
CH₂CH₂;

R¹ and R² are each independently selected from:

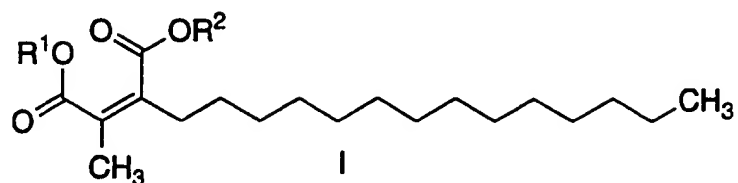
- 15 a) H;
b) C₁₋₅ alkyl;
c) C₁₋₅ alkyl substituted with a member of the group consisting of:
i) phenyl;
20 ii) phenyl substituted with methyl, methoxy, halogen (Cl, Br, F, I) or hydroxy;

or a pharmaceutically acceptable salt of a compound of formula (I) in which at least one of R¹ and R² is hydrogen;

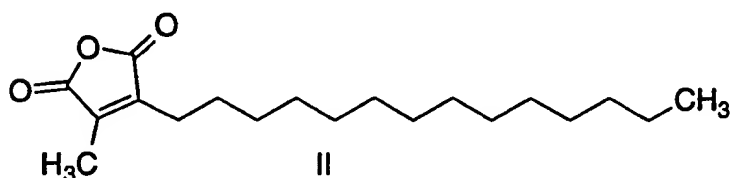
25

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cc) U.S.Pat. No. 5, 420,157, incorporated herein by reference,



or



wherein:

R¹ and R² are each independently selected from:

5

- a) H;
- b) C₁₋₅ alkyl;
- c) C₁₋₅ alkyl substituted with a member of the group consisting of:
 - i) phenyl;
 - ii) phenyl substituted with methyl, methoxy, halogen (Cl, Br, F, I) or hydroxy;

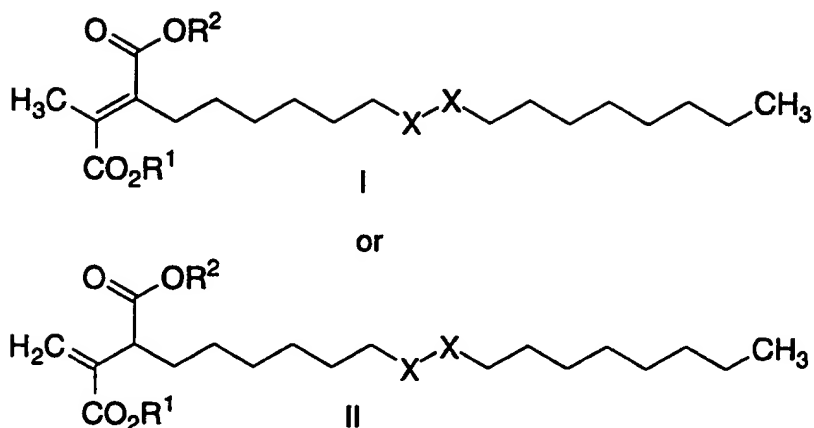
10

or a pharmaceutically acceptable salt of a compound of formula (I) in which at least one of R¹ and R² is hydrogen;

15

dd) U.S.Pat. Nos. 5, 245,061 and 5, 350,867, incorporated herein by reference,

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wherein:

X - X is: CH = CH (cis);
CH = CH (trans); or
CH₂CH₂;

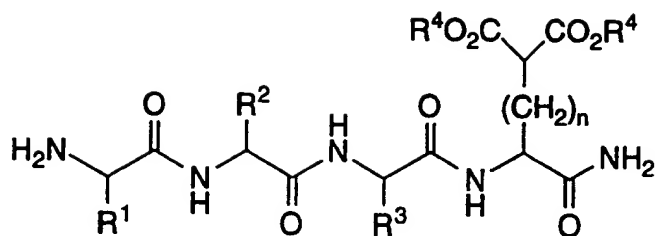
R¹ and R² are each independently selected from:

- a) H;
- b) C₁₋₅ alkyl;
- c) C₁₋₅ alkyl substituted with a member of the group consisting of:
 - i) phenyl;
 - ii) phenyl substituted with methyl, methoxy, halogen (Cl, Br, F, I) or hydroxy;

or a pharmaceutically acceptable salt of a compound of formula (I) in which at least one of R¹ and R² is hydrogen;

ee) PCT Publication WO 96/10037 and US. Serial No. 08/459,885;
incorporated herein by reference;

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I

or the pharmaceutically acceptable salts, hydrates, esters or amides thereof, wherein:

5 n is: 0 to 4,

R¹ and R³ independently are C₀₋₄ alkyl, substituted with substituents selected from the group consisting of:

10 a) aryl, which is defined as phenyl or naphthyl, unsubstituted or substituted with one, two, three or four substituents selected from the group consisting of:

- 15 i) F,
 ii) Cl,
 iii) Br,
 iv) nitro,
 v) cyano,
 vi) C₁₋₈ alkoxy,
 vii) C₁₋₈ alkylthio,
 viii) C₁₋₈ alkylsulfonyl,
 20 ix) sulfamoyl, or
 x) C₁₋₈ alkyl; or

b) heteroaryl, which is defined as indolyl, imidazolyl or pyridyl, unsubstituted or substituted with one, two, three or four substituents selected from the group consisting of:

25

- i) F,
 ii) Cl,
 iii) Br,

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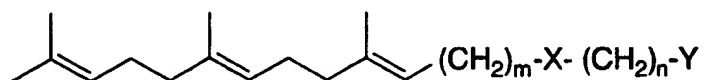
- iv) nitro,
 v) cyano,
 vi) C₁₋₈ alkoxy,
 vii) C₁₋₈ alkylthio,
 5 viii) C₁₋₈ alkylsulfonyl,
 ix) sulfamoyl, or
 x) C₁₋₈ alkyl;

10 R² is: C₀₋₆ alkyl, which is unsubstituted or substituted with a substituent selected from the group consisting of:

- a) unsubstituted or substituted aryl, as defined in R¹(a),
 b) unsubstituted or substituted heteroaryl, as defined in R¹(b),
 c) C₃₋₈ cycloalkyl,
 15 d) C₁₋₈ alkylthio,
 e) C₁₋₈ alkylsulfonyl,
 f) C₁₋₈ alkoxy, or
 g) aryl C₁₋₈ alkyl sulfonyl; and

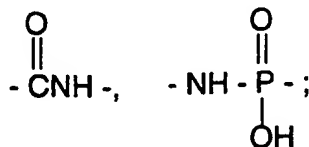
20 R⁴ is: H;

ff) U.S. Pat. Nos. 5,298,655 and 5,362,906; incorporated herein by reference;



25 wherein:

X is CH₂, CH(OH), C=O, CHCOR, CH(NH₂), CH(NHCOR), O, S(O)_p, NH, NHCO,



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p is 0, 1 or 2;

Y is PO_3RR^1 or CO_2R ;R is H, lower alkyl, or $\text{CH}_2\text{CH}_2\text{N}^+\text{Me}_3\text{A}^-$; R^1 is H, lower alkyl, or $\text{CH}_2\text{CH}_2\text{N}^+\text{Me}_3\text{A}^-$;

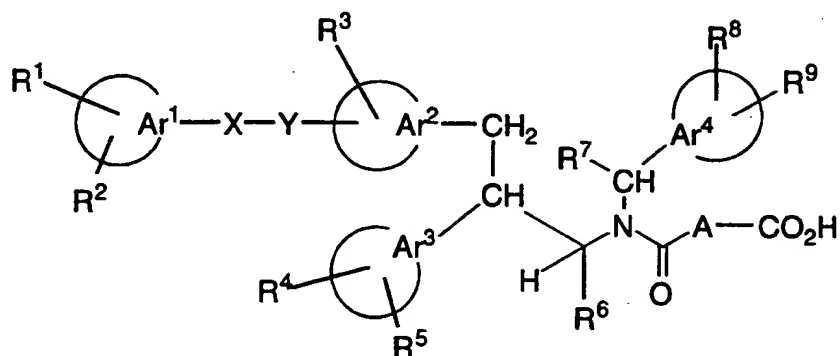
5 A is a pharmaceutically acceptable anion;

m is 0, 1, 2, or 3; and

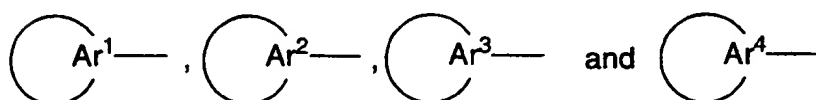
n is 0, 1, 2, or 3;

gg) PCT Publication WO 96/05169, incorporated herein by reference,

10



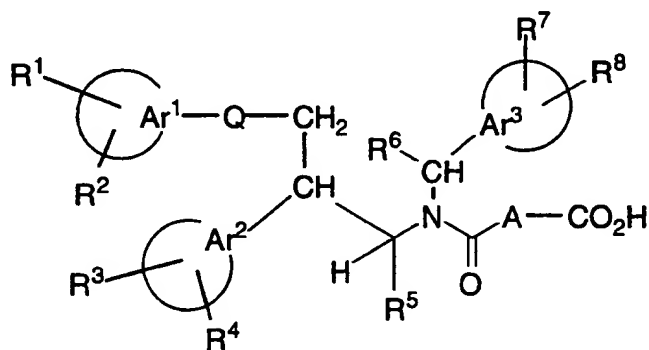
wherein each of



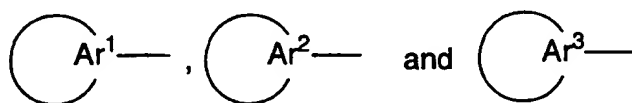
- 15 which are the same or different, is an aryl group or a heteroaromatic ring group; A is a C₂-8 saturated or unsaturated aliphatic hydrocarbon group which may have substituent(s) selected from the group consisting of a lower alkyl group, a hydroxyl group, a lower hydroxyalkyl group, a lower alkoxy group, a carboxyl group, a lower carboxyalkyl group, an aryl group and an aralkyl group; each of X and Y which are the
- 20 same or different, is an oxygen atom, a sulfur atom, a carbonyl group or a group of the formula $-\text{CHR}^a-$ (wherein R^a is a hydrogen atom or a lower alkyl group) or $-\text{NR}^b$ (wherein R^b is a hydrogen atom or a lower alkyl group), or X and Y together represent

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- a vinylene group or an ethynylene group; each of R^1 , R^2 , R^3 , R^8 and R^9 which are the same or different, is a hydrogen atom, a halogen atom, a hydroxyl group, a lower alkyl group or a lower alkoxy group; each of R^4 and R^5 which are the same or different, is a hydrogen atom,
- 5 a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, a carboxyl group, a lower alkoxycarbonyl group, a carbamoyl group, a lower alkylcarbamoyl group, a lower alkyl group, a lower hydroxyalkyl group, a lower fluoroalkyl group or a lower alkoxy group; R^6 is a lower alkyl group; and R^7 is a hydrogen atom or a
- 10 lower alkyl group, provided that when one of X and Y is an oxygen atom, a sulfur atom or a group of the formula $-NR^b$ - (wherein R^b is as defined above), the other is a carbonyl group or a group of the formula $-CHR^a$ - (wherein R^a is as defined above);
- 15 hh) PCT Publication WO 96/05168, incorporated herein by reference,



wherein each of



- 20 which are the same or different, is an aryl group or a heteroaromatic ring group; A is a C2-8 saturated or unsaturated aliphatic hydrocarbon group which may have substituent(s) selected from the group consisting of a lower alkyl group, a hydroxyl group, a lower hydroxyalkyl group,

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a lower alkoxy group, a carboxyl group, a lower carboxyalkyl group, an aryl group and an aralkyl group; Q is a group of the formula $-(CH_2)_m-$ (wherein m is an integer of from 1 to 6) or $-(CH_2)_n-W-(CH_2)_p-$ (wherein W is an oxygen atom, a sulfur atom, a vinylene group or an ethynylene group; and each of n and p which are the same or different, is an integer of from 0 to 3); R^1 is a hydrogen atom, a halogen atom, a hydroxyl group, a lower alkyl group, a lower alkoxy group, or an aryl or heteroaromatic ring group which may have substituent(s) selected from the group consisting of a halogen atom, a lower alkyl group and a lower alkoxy group; each of R^2 , R^7 and R^8 which are the same or different, is a hydrogen atom, a halogen atom, a hydroxyl group, a lower alkyl group or a lower alkoxy group; each of R^3 and R^4 which are the same or different, is a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, a carboxyl group, a lower alkoxycarbonyl group, a carbamoyl group, a lower alkylcarbamoyl group, a lower alkyl group, a lower hydroxyalkyl group, a lower fluoroalkyl group or a lower alkoxy group; R^5 is a lower alkyl group; and R^6 is a hydrogen atom or a lower alkyl group;

or the pharmaceutically acceptable salts thereof.

Specific examples of farnesyl pyrophosphate-competitive inhibitors include:

- 3-Hydroxy-7,11,15-trimethylhexadeca-6,10,14-trienoic acid,
[2- Oxo-6,10,14-trimethylpentadeca-5,9,13-trienyl]phosphonic acid
[2- Hydroxy-6,10,14-trimethylpentadeca-5,9,13-trienyl]phosphonic acid
[1- Acetyl-4,8,12-trimethylpentadeca-3,7,11-trienyl]phosphonic acid

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[2-[(E,E)-3,7,11-Trimethyl-2,6,10-dodecatrienylamino]-2-oxo-ethyl]phosphonic acid

5 [(E,E)-4,8,12-Trimethyl-3,7,11-tridecatrienyl]thiomethyl-phosphonic acid

3-[(E,E)-3,7,11-Trimethyl-2,6,10-dodecatrienylamino]-3-oxo-propionic acid

10 [2-[(E,E)-3,7,11-Trimethyl-2,6,10-dodecatrienylamino]-2-oxo-ethyl]phosphonic acid monomethyl ester

15 [2-[(E,E)-3,7,11-Trimethyl-2,6,10-dodecatrienylamino]-1-oxo-methyl]phosphonic acid

[1-Hydroxy-(E,E)-3,7,11-trimethyl-2,6,10-dodecatrienyl]-phosphonic acid

20 [1-Hydroxy-(E,E)-5,9,13-trimethyl-4,8,12-tetradecatrienyl]-phosphonic acid

[1-Hydroxy-(E,E)-4,8,12-trimethyl-3,7,11-tridecatrienyl]-phosphonic acid

25 [2-Acetamido-(E,E)-4,8,12-trimethyl-3,7,11-tridecatrienyl]-phosphonic acid and

30 [2-Hydroxy-(E,E)-4,8,12-trimethyl-3,7,11-tridecatrienyl]-phosphonic acid

N-{(1R,2R,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

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- N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(1-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid
- 5 N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)pentyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-4-(2-naphthoxy)butyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 10 N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-4-(2-naphthyl)butyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-6-(2-naphthyl)hexyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 15 N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-5-phenyl-4-pentynyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- N-{(1RS,2RS,4E)-2-(4-methoxyphenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 20 N-{(1RS,2RS,4E)-1-methyl-2-(4-methylphenyl)-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- N-{(1RS,2RS,4E)-1-methyl-2-(4-methylphenyl)-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 25 N-{(1RS,2RS,4E)-1-methyl-5-(2-naphthyl)-2-(4-nitrophenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- N-{(1RS,2RS,4E)-2-(4-fluorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 30 N-{(1RS,2RS,4E)-1-methyl-5-(2-naphthyl)-2-(4-trifluoromethylphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

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- N-{(1RS,2RS,4E)-1-methyl-5-(2-naphthyl)-2-phenyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 5 N-{(1RS,2RS,4E)-1-methyl-2-(6-methyl-3-pyridyl)-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- N-{(1RS,2RS,6E)-2-(4-chlorophenyl)-1-methyl-7-phenyl-6-heptenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 10 N-{(1RS,2RS,6E)-2-(4-chlorophenyl)-1-methyl-7-(2-naphthyl)-6-heptenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(3-quinolylmethyl)carbamoylmethylsuccinic acid
- 15 N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(3,4-difluorobenzyl)carbamoylmethylsuccinic acid
- N-(2-benzoxazolylmethyl)-N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}carbamoylmethylsuccinic acid
- 20 N-(2-benzo[b]thienylmethyl)-N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}carbamoylmethylsuccinic acid
- 25 N-{(1RS,2RS,4E)-1-methyl-2-(3,4-methylenedioxyphenyl)-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- (2R*)-2-[N-{(1S*,2S*,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- 30 (2R*)-2-[N-{(1R*,2R*,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

- (2S*)-2-[N-{(1R*,2R*,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- 5 (2S*)-2-[N-{(1S*,2S*,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- 5-[N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]pentanoic acid
- 10 (2R*)-2-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- 15 (2R*)-2-[N-{(1RS,2RS,4Z)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- (2R*)-2-[N-(2-benzo[b]furanylmethyl)-N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}carbamoylmethyl]succinate
- 20 (2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}carbamoylmethyl]succinic acid
- 25 (2R*)-2-[N-[(1RS,2RS,4E)-5-(2-benzoxazolyl)-2-{3,4-bis(methoxycarbonyl)phenyl}-1-methyl-4-pentenyl]-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- 30 (2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methyl-4-pentenyl}carbamoylmethyl]succinic acid

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- (2R*)-2-[N-(2-benzo[b]furanylmethyl)-N-{(1R,2R,4E)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methyl-4-pentenyl}carbamoylmethyl]succinic acid
- 5 (2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-{(1R,2R,4E)-5-(2-benzoxazolyl)-2-(4-cyanophenyl)-1-methyl-4-pentenyl}carbamoylmethyl]succinic acid
- 10 (2R*)-2-[N-(5-benzo[b]thienylmethyl)-N-{(1R,2R,4E)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methyl-4-pentenyl}carbamoylmethyl]succinic acid
- 15 N-{(1R,2R,4E)-5-(3-chloro-4-methylphenyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- N-{(1R,2R,4Z)-5-(3-chloro-4-methylphenyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 20 N-{(1R,2R,4E)-5-(2-benzo[b]furanyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- N-{(1R,2R,4Z)-5-(2-benzo[b]furanyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 25 N-{(1R,2R,4E)-5-(2-benzoxazolyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- N-{(1R,2R,4Z)-5-(2-benzoxazolyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 30 N-{(1R,2R,4E)-5-(2-benzimidazolyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

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N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

- 5 N-{(1RS,2RS,4E)-5-(2-benzothiazolyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-2-(4-cyanophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

10

4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-1,2,3-butanetricarboxylic acid

- 15 3-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-1,2,2-propanetricarboxylic acid

- 20 (2S,3R)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]-3-carboxy-2-hydroxybutanoic acid

- 25 4-[N-((1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl)-N-(2-naphthylmethyl)carbamoyl]-3-carboxy-4-methoxybutanoic acid

- 5-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-4-carboxy-3-carboxymethylpentanoic acid

30

1-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-1,2,3-propanetricarboxylic acid

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- (3R*)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-methoxybutanoic acid
- 5 (3S*)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-methoxybutanoic acid
- 10 N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-2-(4-carboxyphenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 15 N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-{4-(N-methylcarbamoyl)phenyl}-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- (2R*)-2-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-2-(4-hydroxy-3-methoxyphenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 20 N-{(1RS,2RS,4E)-2-(4-hydroxymethylphenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 25 N-{(1RS,2RS,4E)-2-(4-aminophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- disodium (3RS,4RS)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxy-4-hydroxybutanoate
- 30 N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)-5-oxotetrahydrofuran-2-carboxamide

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sodium 4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)]carbamoyl-4-hydroxybutanoate

5 4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-2-oxotetrahydrofuran-3-yl-acetic acid

(2R*)-2-[N-{(1R*,2R*,4E)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

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(2R*)-2-[N-{(1S*,2S*,4E)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

15

(2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-{(1S*,2S*,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}carbamoylmethyl]succinic acid

20

(2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-{(1R*,2R*,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}carbamoylmethyl]succinic acid

25 (2R*)-2-[N-{(1RS,2RS)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)pentyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

(2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-{(1RS,2RS)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)pentyl}carbamoylmethyl]succinic acid

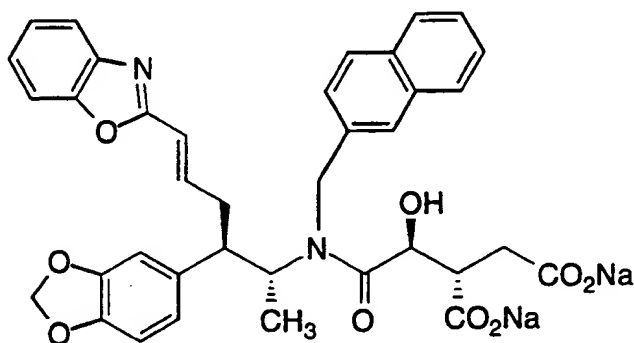
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(2R*)-2-[N-{(1R*,2R*)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methylpentyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

- 5 disodium (3S,4S)-4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxy-4-hydroxybutanoate (Compound D)

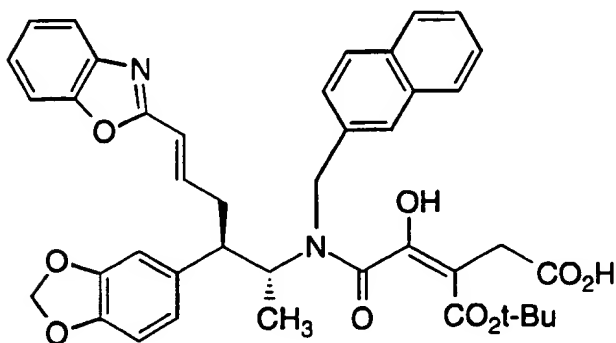
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- sodium (3S,4S)-4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-ethoxycarbonyl-4-hydroxybutanoate
- 15

4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxy-3-butenic acid

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4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
5 4-hydroxy-3-methoxycarbonyl-3-butenic acid

4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
10 4-hydroxy-3-isopropoxycarbonyl-3-butenic acid

4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
3-cyclohexyloxycarbonyl-4-hydroxy-3-butenic acid

15 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
4-hydroxy-3-(2-methoxyethoxy)carbonyl-3-butenic acid

20 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
3-benzyloxycarbonyl-4-hydroxy-3-butenic acid

4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
25 3-cyclopentyloxycarbonyl-4-hydroxy-3-butenic acid

4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
4-hydroxy-3-(3-tetrahydrofuryloxycarbonyl)-3-butenic acid

30 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
4-hydroxy-3-(2-hydroxy-1-hydroxymethylethoxycarbonyl)-3-butenic
acid

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- 3-allyloxycarbonyl-4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-4-hydroxy-3-butenic acid
- 5 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-2-(3,4-methylenedioxyphenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxymethylcarbonyl-4-hydroxy-3-butenic acid
- 10 5-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-4-ethoxycarbonyl-5-hydroxy-4-pentenoic acid
- 15 5-N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-4-tert-butoxycarbonyl-5-hydroxy-4-pentenoic acid
- 20 4-N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-4-hydroxy-3-hydroxymethyl-3-butenic acid
- 25 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-5-hexenyl}-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxy-3-butenic acid
- (2S*,3R*)-4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-1,2,3-butanetricarboxylic acid
- 30 (2R*,3S*)-4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-1,2,3-butanetricarboxylic acid

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N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

5 N-[(1RS,2RS)-3-{5-(3,4-dimethoxyphenylcarbamoyl)-2-furyl}-1-methyl-2-(4-nitrophenyl)propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

10 N-[(1RS,2RS)-3-{5-(2-hydroxyphenylcarbamoyl)-2-furyl}-1-methyl-2-(4-nitrophenyl)propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

N-[(1RS,2RS)-1-methyl-3-{5-(N-methylphenylcarbamoyl)-2-furyl}-2-(4-nitrophenyl)propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

15 N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(3-pyridylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

20 N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(4-pyridylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

25 N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(5-pyrimidinylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(2-thiazolylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

30 N-[(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

N-[(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-3-(3-phenylcarbamoylphenyl)propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

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N-[(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-3-{3-(phenylcarbamoyl)-5-isoxazolyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

5 N-[(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-3-{4-(phenylcarbamoyl)-2-pyridyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

(2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-[(1RS,2RS)-1-methyl-2-(3,4-methylenedioxyphenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]carbamoylmethyl]succinic acid

10

(2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-[(1RS,2RS)-1-methyl-2-(3,4-methylenedioxyphenyl)-3-{5-(3-pyridylcarbamoyl)-2-furyl}propyl]carbamoylmethyl]succinic acid

15

monopivaloyloxymethyl (2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-[(1RS,2RS)-1-methyl-2-(3,4-methylenedioxyphenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]carbamoylmethyl]succinate

20 (2R*)-2-[N-{(1RS,2RS)-2-(4-methoxycarbonylphenyl)-1-methyl-3-(3-phenoxyethylphenyl)propyl}-N-2-naphthylmethyl]carbamoylmethyl]succinic acid

(2R*)-2-[N-[(1RS,2RS)-2-(4-methoxycarbonylphenyl)-1-methyl-3-{3-(phenoxyethyl)-5-(1,2,4-oxadiazolyl)}propyl]-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

25

(2R*)-2-[N-[(1RS,2RS)-2-(4-methoxycarbonylphenyl)-1-methyl-3-{(E)-3-styrylphenyl}propyl]-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

30

(2R*)-2-[N-[(1RS,2RS)-2-(4-methoxycarbonylphenyl)-1-methyl-3-{3-(2-phenylethyl)phenyl}propyl]-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

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N-[(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-3-(4-phenylethynylphenyl)-propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

- 5 N-[(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-3-{(E)-3-styrylphenyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

- 10 N-[(1RS,2RS)-2-(4-methoxycarbonylphenyl)-1-methyl-3-(5-phenoxyethyl-2-furyl)propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

- 15 4-[N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]-1,2,3-butanetricarboxylic acid

- 20 disodium (3RS,4RS)-3-carboxylato-4-hydroxy-4-[N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]butanoate

disodium (3SR,4SR)-3-carboxylato-4-hydroxy-4-[N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]butanoate

- 25 3-tert-butoxycarbonyl-4-hydroxy-4-[N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]-3-butenic acid

- 30 3-tert-butoxycarbonyl-4-hydroxy-4-[N-[(1RS,2RS)-1-methyl-2-(3,4-methylenedioxyphenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]-3-butenic acid

3-tert-butoxycarbonyl-4-hydroxy-4-[N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-(3-phenoxyethylphenyl)propyl]-N-(2-

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naphthylmethyl)carbamoyl]-3-butenic acid

4-hydroxy-3-methoxycarbonyl-4-[N-[(1RS,2RS)-1-methyl-2-(3,4-methylenedioxyphenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]-3-butenic acid

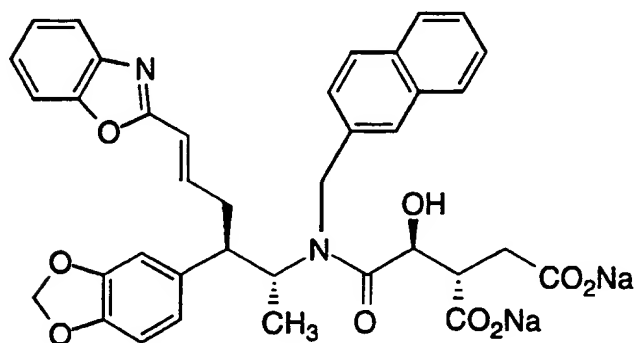
3-allyloxycarbonyl-4-hydroxy-4-[N-[(1RS,2RS)-1-methyl-2-(3,4-methylenedioxyphenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]-3-butenic acid

5-hydroxy-4-isopropylcarbonyl-5-[N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]-4-pentenoic acid

3-tert-butoxycarbonyl-4-{N-(2,3-dichlorobenzyl)-N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]carbamoyl}-4-hydroxy-3-butenic acid

or a pharmaceutically acceptable salt or optical isomer thereof.

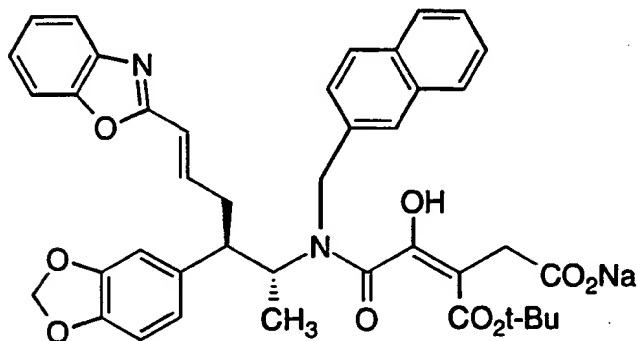
A further embodiment of the specific farnesyl pyrophosphate-competitive inhibitors includes:
disodium (3RS,4RS)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxyl-4-hydroxybutanoate (Compound D)



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and
 sodium 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxy-3-butenate (Compound C)

5



The composition of the instant invention may alternatively
 10 or in addition comprise a farnesyl pyrophosphate-competitive inhibitor
 obtained by fermentation of cultures of novel organisms. In particular,
 the compounds disclosed in the following patents and publications may
 be useful as a farnesyl pyrophosphate-competitive inhibitor component
 of the instant composition: U.S. Ser. Nos. 08/ 254,228 and 08/435,047.
 15 Those patents and publications are incorporated herein by reference.

In addition, compounds described in the following patents
 and publications may also be utilized as a farnesyl pyrophosphate-
 competitive inhibitor component of the instant composition: European
 Pat. Publ. 0 537 008; European Pat. Publ. 0 540 782; PCT Pat. Publs.
 20 WO 94/1935; WO 95/12572 ; and WO 95/08546. Those patents and
 publications are incorporated herein by reference.

The protein substrate-competitive inhibitors and farnesyl
 pyrophosphate-competitive inhibitors of the present invention may have
 25 asymmetric centers and occur as racemates, racemic mixtures, and as
 individual diastereomers, with all possible isomers, including optical
 isomers, being included in the present invention. Unless otherwise

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specified, named amino acids are understood to have the natural "L" stereoconfiguration.

- 5 The following definitions apply to compounds of the general formulas a) through ff) hereinabove:

 As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms.

- 10 As used herein, "cycloalkyl" is intended to include non-aromatic cyclic hydrocarbon groups having the specified number of carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

- "Alkenyl" groups include those groups having the specified number of carbon atoms and having one or several double bonds.
15 Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, isoprenyl, farnesyl, geranyl, geranylgeranyl and the like.

- As used herein, "aryl" is intended to include any stable
20 monocyclic, bicyclic or tricyclic carbon ring(s) of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of aryl groups include phenyl, naphthyl, anthracenyl, biphenyl, tetrahydronaphthyl, indanyl, phenanthrenyl and the like.

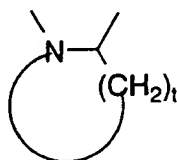
- The term heterocycle or heterocyclic, as used herein,
25 represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic or stable 11-15 membered tricyclic heterocycle ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which
30 any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl,

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benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl,
 benzoxazolyl, chromanyl, cinnoliny, dihydrobenzofuryl, dihydro-
 benzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl
 sulfone, furyl, imidazolidinyl, imidazoliny, imidazolyl, indoliny,
 5 indolyl, isochromanyl, isoindoliny, isoquinoliny, isothiazolidinyl,
 isothiazolyl, isothiazolidinyl, morpholiny, naphthyridiny, oxadiazolyl,
 2-oxoazepiny, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidinyl,
 piperidyl, piperaziny, pyridyl, pyridyl N-oxide, pyridonyl, pyraziny,
 pyrazolidinyl, pyrazolyl, pyrimidinyl, pyrrolidinyl, pyrrolyl,
 10 quinazoliny, quinoliny, quinoliny N-oxide, quinoxaliny,
 tetrahydrofuryl, tetrahydroisoquinoliny, tetrahydro-quinoliny,
 thiamorpholiny, thiamorpholiny sulfoxide, thiazolyl, thiazoliny,
 thienofuryl, thienothienyl, and thienyl.

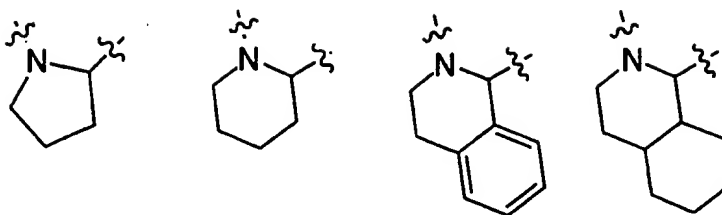
As used herein, the terms "substituted aryl", "substituted
 15 heterocycle" and "substituted cycloalkyl" are intended to include the
 cyclic group which is substituted with 1 or 2 substituents selected from
 the group which includes but is not limited to F, Cl, Br, CF₃, NH₂,
 N(C₁-C₆ alkyl)₂, NO₂, CN, (C₁-C₆ alkyl)O-, -OH, (C₁-C₆
 alkyl)S(O)_m-, (C₁-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, (C₁-C₆
 20 alkyl)C(O)-, (C₁-C₆ alkyl)OC(O)-, N₃, (C₁-C₆ alkyl)OC(O)NH- and
 C₁-C₂₀ alkyl.

The following structure:



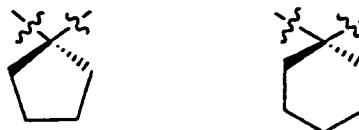
25 represents a cyclic amine moiety having 5 or 6 members in the ring,
 such a cyclic amine which may be optionally fused to a phenyl or
 cyclohexyl ring. Examples of such a cyclic amine moiety include, but
 are not limited to, the following specific structures:

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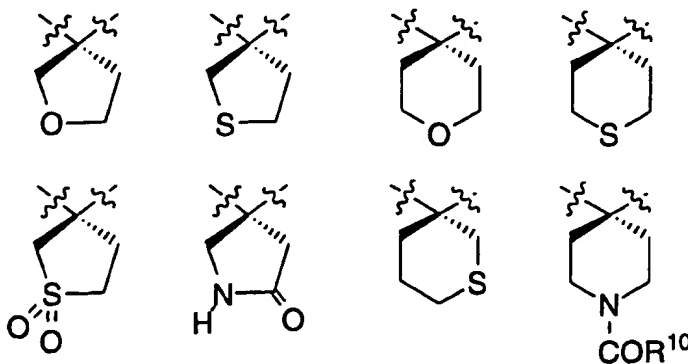
It is also understood that substitution on the cyclic amine moiety by R^{2a}, R^{2b}, R^{7a} and R^{7b} may be on different carbon atoms or on the same
 5 carbon atom.

When R^{2a} and R^{2b}, and R³ and R⁴ are combined to form - (CH₂)_s -, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:



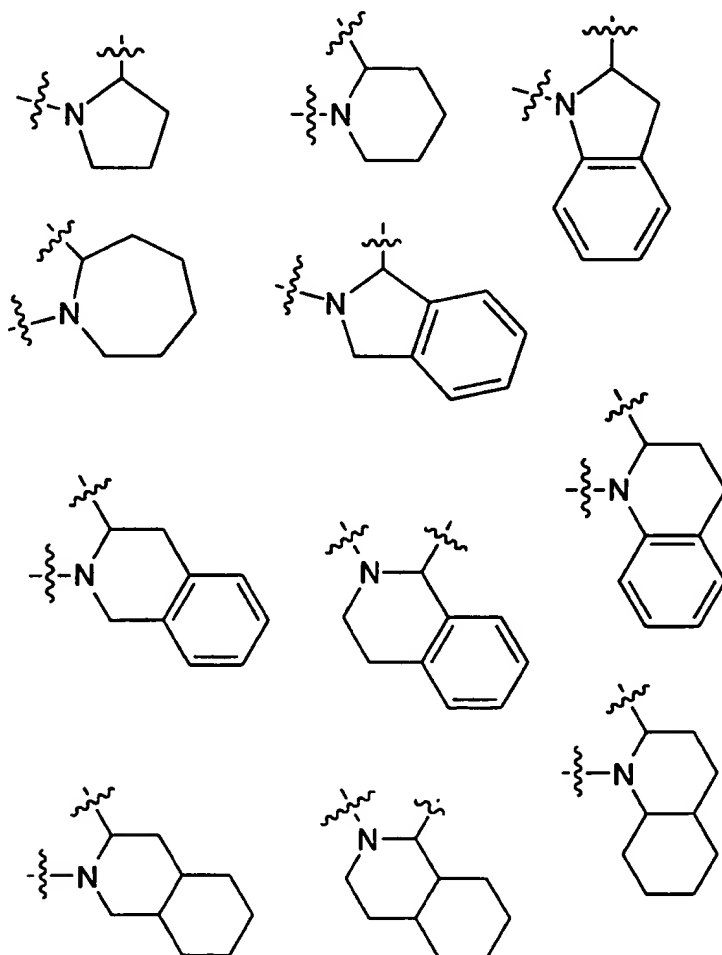
10

When R^{5a} and R^{5b} are combined to form - (CH₂)_s -, cyclic moieties as described hereinabove for R³ and R⁴ are formed. In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are
 15 not limited to:



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As used herein, the phrase "nitrogen containing C4-C9 mono or bicyclic ring system wherein the non-nitrogen containing ring may be a C6 aromatic ring, a C5-C7 saturated ring or a heterocycle" which defines moiety "Q" of the instant invention includes but is not
5 limited to the following ring systems:



It is intended that the definition of any substituent or
10 variable (e.g., R¹⁰, Z, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, -N(R¹⁰)₂ represents -NHH, -NHCH₃, -NHC₂H₅, etc. It is understood that substituents and substitution patterns on the protein substrate-competitive inhibitors and farnesyl pyrophosphate-competitive

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inhibitors of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth below.

5 The pharmaceutically acceptable salts of the protein substrate-competitive inhibitors and farnesyl pyrophosphate-competitive inhibitors of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic
10 inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenyl-acetic, glutamic, benzoic, salicylic, sulfanilic, 2-
15 acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

 The pharmaceutically acceptable salts of the protein substrate-competitive inhibitors and farnesyl pyrophosphate-competitive inhibitors of this invention can be synthesized from the corresponding
20 inhibitor of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

25 The following definitions apply to compounds of the general formulas gg) through hh) hereinabove:

 The aryl group means a phenyl group, a naphthyl group or an anthryl group. A phenyl group or a naphthyl group is preferred.

30 The heteroaromatic ring group means a 5-membered or 6-membered monocyclic aromatic heterocyclic group containing one or two heteroatoms, which are the same or different, selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, or a fused aromatic heterocyclic group having such a monocyclic

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aromatic heterocyclic group fused with the above-mentioned aryl group or having the same or different such monocyclic aromatic heterocyclic groups fused with each other, which may, for example, be a pyrrolyl group, an imidazolyl group, a pyrazolyl group, a pyridyl group, a pyrazinyl group, a pyrimidinyl group, a pyridazinyl group, an oxazolyl group, an isoxazolyl group, a furyl group, a thienyl group, a thiazolyl group, an isothiazolyl group, an indolyl group, a benzofuranyl group, a benzothienyl group, a benzimidazolyl group, a benzoxazolyl group, a benzisoxazolyl group, a benzothiazolyl group, a benzisothiazolyl group, an indazolyl group, a purinyl group, a quinolyl group, an isoquinolyl group, a phthalazinyl group, a naphthylidinyl group, a quinoxaliny group, a quinazolinyl group, a cinnolinyl group or a pteridinyl group. Among them, a furyl group, a thienyl group, a pyridyl group, a pyrimidinyl group, an oxazolyl group, an isoxazolyl group, a thiazolyl group, a benzofuranyl group, a benzothienyl group, a benzimidazolyl group, a benzoxazolyl group, a benzothiazolyl group or a quinolyl group is preferred.

The lower alkyl group means a C₁-6 linear or branched alkyl group, which may, for example, be a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, a sec-butyl group, a tert-butyl group, a pentyl group or a hexyl group. Among them, a methyl group or an ethyl group is preferred.

The lower hydroxyalkyl group means the above-mentioned lower alkyl group having a hydroxyl group, i.e. a C₁-6 hydroxyalkyl group, such as a hydroxymethyl group, a hydroxyethyl group, a hydroxypropyl group or a hydroxybutyl group. Among them, a hydroxymethyl group or a hydroxyethyl group is preferred.

The lower alkoxy group means a C₁-6 alkoxy or alkylendioxy group, which may, for example, be a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, a tert-butoxy group, a methylenedioxy group, an ethylenedioxy group or a trimethylenedioxy group. Among them, a methoxy group, an ethoxy group or a methylenedioxy group is preferred.

The lower carboxyalkyl group means the above-

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mentioned lower alkyl group having a carboxyl group, i.e. a C₁₋₇ carboxyalkyl group, such as a carboxymethyl group, a carboxyethyl group, a carboxypropyl group or a carboxybutyl group. Among them, a carboxymethyl group or a carboxyethyl group is preferred.

5 The aralkyl group means the above-mentioned lower alkyl group having the above-mentioned aryl group, such as a benzyl group, a phenethyl group, a 3-phenylpropyl group, a 1-naphthylmethyl group, a 2-naphthylmethyl group or a 1-(2-naphthyl)ethyl group. Among them, a benzyl group, a phenethyl group or a 2-naphthylmethyl group is preferred.

10 The saturated aliphatic hydrocarbon group may, for example, be an ethylene group, a trimethylene group, a tetramethylene group, a pentamethylene group, a hexamethylene group, a heptamethylene group or an octamethylene group. For example, a trimethylene group, a tetramethylene group or a pentamethylene group is preferred.

 The unsaturated aliphatic hydrocarbon group means an unsaturated aliphatic hydrocarbon group having one or more, preferably one or two double bonds, at optional position(s) on the carbon chain, which may, for example, be a vinylene group, a propenylene group, a 1-butenylene group, a 2-butenylene group, a 1,3-butadienylene group, a 1-pentenylene group, a 2-pentenylene group, a 1,3-pentadienylene group, a 1,4-pentadienylene group, a 1-hexenylene group, a 2-hexenylene group, a 3-hexenylene group, a 1,3-hexadienylene group, a 1,4-hexadienylene group, a 1,5-hexadienylene group, a 1,3,5-hexatrienylene group, a 1-heptenylene group, a 2-heptenylene group, a 3-heptenylene group, a 1,3-heptadienylene group, a 1,4-heptadienylene group, a 1,5-heptadienylene group, a 1,6-heptadienylene group, a 1,3,5-heptatrienylene group, a 1-octenylene group, a 2-octenylene group, a 3-octenylene group, a 4-octenylene group, a 1,3-octadienylene group, a 1,4-octadienylene group, a 1,5-octadienylene group, a 1,6-octadienylene group, a 1,7-octadienylene group, a 2,4-octadienylene group, a 2,5-octadienylene group, a 2,6-

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octadienylene group, a 3,5-octadienylene group, a 1,3,5-octatrienylene group, a 2,4,6-octatrienylene group or a 1,3,5,7-octatetraenylene group. Among them, a propenylene group, a 1-butenylene group, a 1,3-butadienylene group or a 1-pentenylene group is preferred.

5 The halogen atom may be a fluorine atom, a chlorine atom, a bromine atom or an iodine atom. For example, a fluorine atom or a chlorine atom is preferred.

 The lower alkoxycarbonyl group means a C₁-7
alkoxycarbonyl group, such as a methoxycarbonyl group, an
10 ethoxycarbonyl group, a propoxycarbonyl group, a butoxycarbonyl group or a tert-butoxycarbonyl group. Among them, a methoxycarbonyl group or an ethoxycarbonyl group is preferred.

 The lower alkylcarbamoyl group means a carbamoyl
group mono-substituted or di-substituted by the above-mentioned lower
15 alkyl group, such as a methylcarbamoyl group, an ethylcarbamoyl group, a dimethylcarbamoyl group or a diethylcarbamoyl group.

 The lower fluoroalkyl group means the above-mentioned
lower alkyl group having fluorine atom(s), i.e. a C₁-6 fluoroalkyl
group, such as a fluoromethyl group, a difluoromethyl group, a
20 trifluoromethyl group, a 1-fluoroethyl group, a 2-fluoroethyl group, a 2,2,2-trifluoroethyl group or a pentafluoroethyl group.

 The salt of the compound of the formula (gg) or (hh) may
be a pharmaceutically acceptable common salt, which may, for example,
25 be a base-addition salt of the terminal carboxyl group or of a carboxyl group when R⁴ and/or R⁵ or R³ and/or R⁴ is a carboxyl group, or when a carboxyl group or a lower carboxyalkyl group is present on a saturated or unsaturated aliphatic hydrocarbon group represented by A in the formulas (gg) and (hh), or an acid-addition salt of an amino
30 group when R⁴ and/or R⁵ or R³ and/or R⁴ is an amino group, or of a basic heteroaromatic ring when such a basic heteroaromatic ring is present.

 The base-addition salt may, for example, be an alkali metal salt such as a sodium salt or a potassium salt; an alkaline earth metal salt

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such as a calcium salt or a magnesium salt; an ammonium salt; or an organic amine salt such as a trimethylamine salt, a triethylamine salt, a dicyclohexylamine salt, an ethanolamine salt, a diethanolamine salt, a triethanolamine salt, a procaine salt or an N,N'-dibenzylethylenediamine salt.

The acid-addition salt may, for example, be an inorganic acid salt such as a hydrochloride, a sulfate, a nitrate, a phosphate or a perchlorate; an organic acid salt such as a maleate, a fumarate, a tartrate, a citrate, an ascorbate or a trifluoroacetate; or a sulfonic acid salt such as a methanesulfonate, an isethionate, a benzenesulfonate or a p-toluenesulfonate.

The ester of the compound of the formula (gg) or (hh) means a pharmaceutically acceptable common ester of the terminal carboxyl group or of a carboxyl group when R⁴ and/or R⁵ or R³ and/or R⁴ is a carboxyl group, or when a carboxyl group or a lower carboxyalkyl group is present on the saturated or unsaturated aliphatic hydrocarbon group represented by A in the formulas (gg) and (hh). It may, for example, be an ester with a lower alkyl group such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, a sec-butyl group, a tert-butyl group, a cyclopropyl group or a cyclopentyl group, an ester with an aralkyl group such as a benzyl group or a phenethyl group, an ester with a lower alkenyl group such as an allyl group or a 2-butenyl group, an ester with a lower alkoxyalkyl group such as a methoxymethyl group, a 2-methoxyethyl group or a 2-ethoxyethyl group, an ester with a lower alkanoyloxyalkyl group such as an acetoxymethyl group, a pivaloyloxymethyl group or a 1-pivaloyloxyethyl group, an ester with a lower alkoxycarbonylalkyl group such as a methoxycarbonylmethyl group or an isopropoxycarbonylmethyl group, an ester with a lower carboxyalkyl group such as a carboxymethyl group, an ester with a lower alkoxycarbonyloxyalkyl group such as a 1-(ethoxycarbonyloxy)ethyl group or a 1-(cyclohexyloxy)ethyl group, an ester with a lower carbamoyloxyalkyl group such as a carbamoyloxymethyl group, an ester with a phthalidyl group, or an ester with a (5-substituted-2-oxo-

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1,3-dioxol-4-yl)methyl group such as a (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group.

Further, when a hydroxyl group is present at the γ - or δ -position of the terminal carboxyl group or of a carboxyl group when such a carboxyl group or a lower carboxyalkyl group is present on the saturated or unsaturated aliphatic hydrocarbon group represented by A in the formulas (gg) and (hh), such a hydroxyl group and a carboxyl group may form an intramolecular ester i.e. a 5-membered or 6-membered lactone ring.

Further, the compound of the present invention may have stereoisomers such as optical isomers, diastereomers or geometrical isomers, depending upon the form of its substituents. The compound of the present invention includes all of such stereoisomers and their mixtures.

Further, the compound of the present invention may have enol form and keto form tautomers, depending upon the form of its substituents. The compounds of the present invention includes such enol form and keto form isomers and their mixtures.

Some of the protein substrate-competitive inhibitors and farnesyl pyrophosphate-competitive inhibitors of the invention can be synthesized from their constituent amino acids by conventional peptide synthesis techniques, and the additional methods described below. Standard methods of peptide synthesis are disclosed, for example, in the following works: Schroeder *et al.*, "*The Peptides*", Vol. I, Academic Press 1965, or Bodanszky *et al.*, "*Peptide Synthesis*", Interscience Publishers, 1966, or McOmie (ed.) "*Protective Groups in Organic Chemistry*", Plenum Press, 1973, or Barany *et al.*, "*The Peptides: Analysis, Synthesis, Biology*" 2, Chapter 1, Academic Press, 1980, or Stewart *et al.*, "*Solid Phase Peptide Synthesis*", Second Edition, Pierce Chemical Company, 1984. Also useful in exemplifying syntheses of specific unnatural amino acid residues are European Pat. Appl. No. 0 350 163 A2 (particularly page 51-52) and J. E. Baldwin *et al.* *Tetrahedron*, 50:5049-5066 (1994). With regards to the synthesis of instant compounds containing a (β -acetylamino)alanine residue at the C-

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terminus, use of the commercially available N α -Z-L-2,3-diaminopropionic acid (Fluka) as a starting material is preferred. The teachings of these works are hereby incorporated by reference.

Abbreviations used in the description of the chemistry and
5 in the Examples that follow are:

	Ac ₂ O	Acetic anhydride;
	Boc	t-Butoxycarbonyl;
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;
10	DMAP	4-Dimethylaminopyridine;
	DME	1,2-Dimethoxyethane;
	DMF	Dimethylformamide;
	EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride;
15	HOBT	1-Hydroxybenzotriazole hydrate;
	Et ₃ N	Triethylamine;
	EtOAc	Ethyl acetate;
	FAB	Fast atom bombardment;
	HOObt	3-Hydroxy-1,2,2-benzotriazin-4(3H)-one;
20	HPLC	High-performance liquid chromatography;
	MCPBA	m-Chloroperoxybenzoic acid;
	MsCl	Methanesulfonyl chloride;
	NaHMDS	Sodium bis(trimethylsilyl)amide;
	Py	Pyridine;
25	TFA	Trifluoroacetic acid;
	THF	Tetrahydrofuran.

The protein substrate-competitive inhibitors of this invention designated "v)" hereinabove are prepared by employing the
30 reactions shown in the following Reaction Schemes A-R, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Such Reaction Schemes are also useful in preparing other protein substrate-competitive inhibitors

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and farnesyl pyrophosphate-competitive inhibitors. For example, Reaction Schemes A-E are especially useful in preparing the inhibitors designated "a)" through "k)", "m)", "n)", "q)" through "u)" and "ee)" hereinabove. Some key bond-forming and peptide modifying reactions are:

Reaction A Amide bond formation and protecting group cleavage using standard solution or solid phase methodologies.

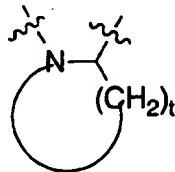
Reaction B Preparation of a reduced peptide subunit by reductive alkylation of an amine by an aldehyde using sodium cyanoborohydride or other reducing agents.

Reaction C Alkylation of a reduced peptide subunit with an alkyl or aralkyl halide or, alternatively, reductive alkylation of a reduced peptide subunit with an aldehyde using sodium cyanoborohydride or other reducing agents.

Reaction D Peptide bond formation and protecting group cleavage using standard solution or solid phase methodologies.

Reaction E Preparation of a reduced subunit by borane reduction of the amide moiety.

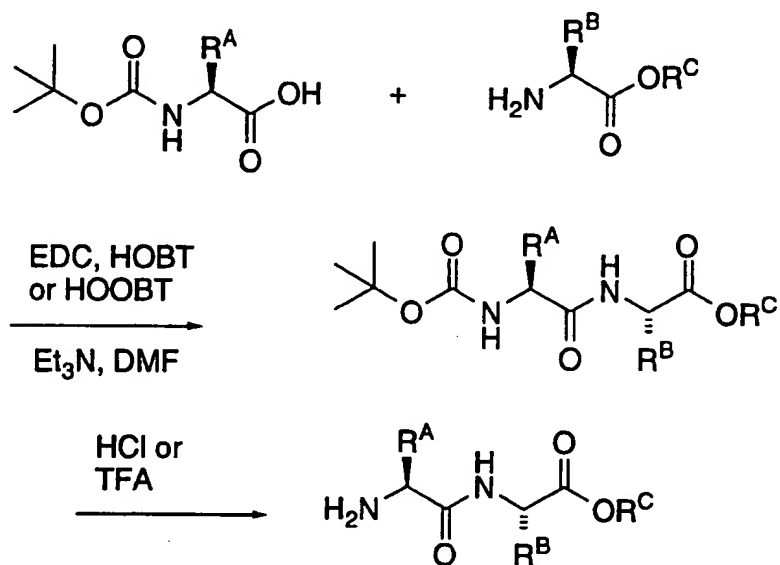
Reaction Schemes A-E illustrate bond-forming and peptide modifying reactions incorporating acyclic peptide units. It is well understood that such reactions are equally useful when the -NHC(R^A)- moiety of the reagents and compounds illustrated is replaced with the following moiety:



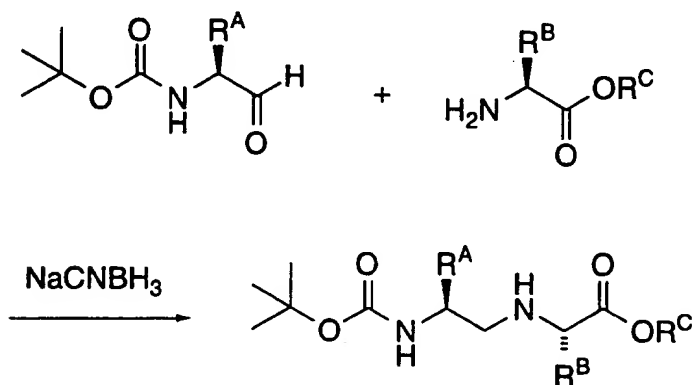
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These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Reaction Schemes.

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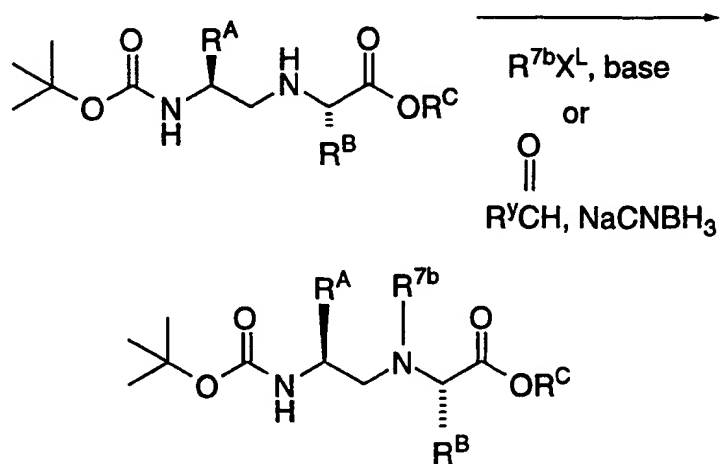
REACTION SCHEME AReaction A. Coupling of residues to form an amide bond

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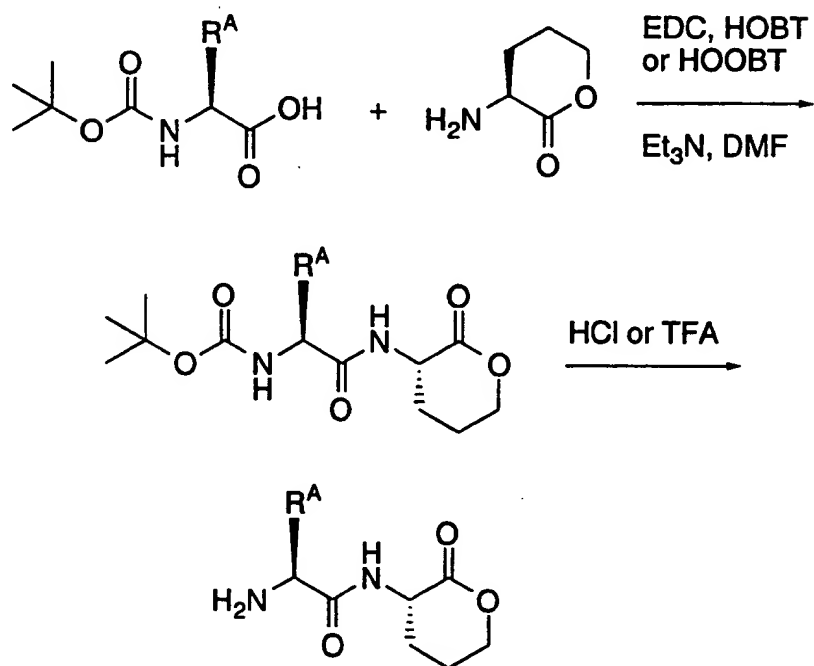
REACTION SCHEME BReaction B. Preparation of reduced peptide subunits by reductive alkylation

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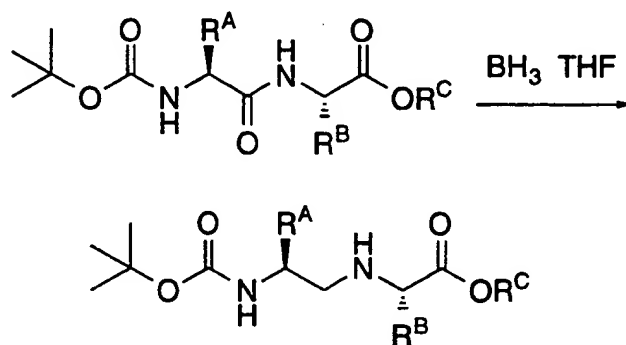
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REACTION SCHEME CReaction C. Alkylation/reductive alkylation of reduced peptide subunits

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REACTION SCHEME DReaction D. Coupling of residues to form an amide bond

5

REACTION SCHEME EReaction E. Preparation of reduced dipeptides from peptides

10 where R^A and R^B are R^3 , R^4 , R^{5a} or R^{5b} as previously defined; R^C is R^6 as previously defined or a carboxylic acid protecting group; XL is a

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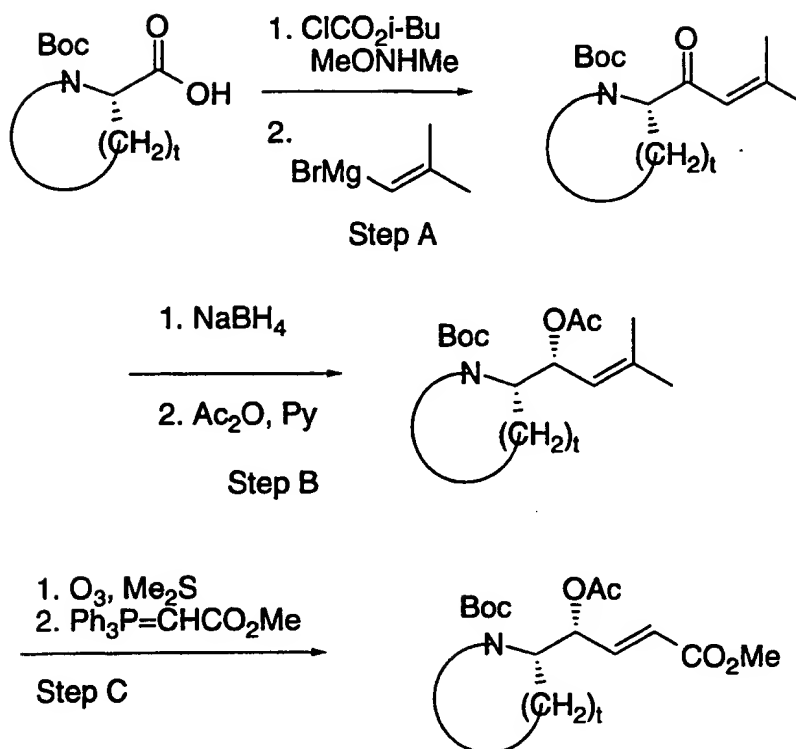
leaving group, e.g., Br⁻, I⁻ or MsO⁻; and RY is defined such that R^{7b} is generated by the reductive alkylation process.

Certain compounds of this invention wherein X-Y is an ethenylene or ethylene unit are prepared by employing the reaction sequences shown in Reaction Schemes F and G. Reaction Scheme F outlines the preparation of the alkene isosteres utilizing standard manipulations such as Weinreb amide formation, Grignard reaction, acetylation, ozonolysis, Wittig reaction, ester hydrolysis, peptide coupling reaction, mesylation, cleavage of peptide protecting groups, reductive alkylation, etc., as may be known in the literature or exemplified in the Experimental Procedure. For simplicity, substituents R^{2a} and R^{2b} on the cyclic amine moiety are not shown. It is, however, understood that the reactions illustrated are also applicable to appropriately substituted cyclic amine compounds. The key reactions are: stereoselective reduction of the Boc-amino-enone to the corresponding syn amino-alcohol (Scheme F, Step B, Part 1), and stereospecific boron trifluoride or zinc chloride activated organo-magnesium, organo-lithio, or organo-zinc copper(I) cyanide S_N2' displacement reaction (Scheme F, Step G). Through the use of optically pure N-Boc amino acids as starting material and these two key reactions, the stereo-chemistry of the final products is well defined. In Step H of Scheme F, the amino terminus sidechain, designated R^x is incorporated using coupling reaction A and R^xCOOH; the alkylation reaction C using R^xCHO and a reducing agent; or alkylation reaction C using R^xCH₂XL. Such reactions as described in Step H are described in more detail in Reaction Schemes J-X hereinbelow.

The alkane analogs are prepared in a similar manner by including an additional catalytic hydrogenation step as outlined in Reaction Scheme G.

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REACTION SCHEME F

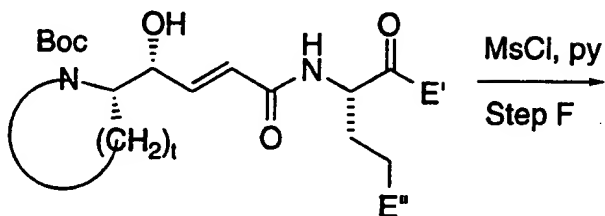
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REACTION SCHEME F (CONT'D)

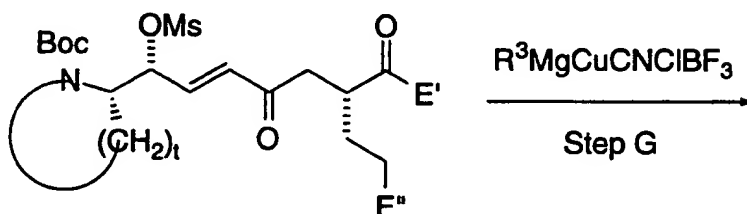
Step D
1. LiOH

Step E
2. EDC, HOBT
amino acid (ester)

$E' = \text{OMe}, E'' = \text{SMe}$
 $E' - E'' = \text{O}$

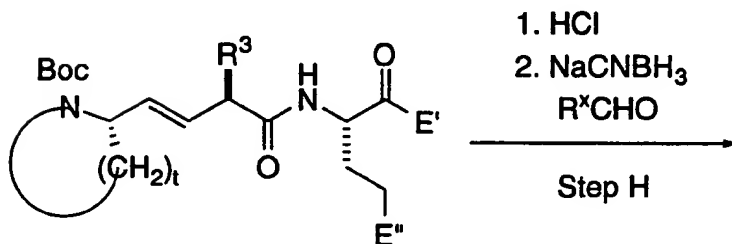


MsCl, py
Step F



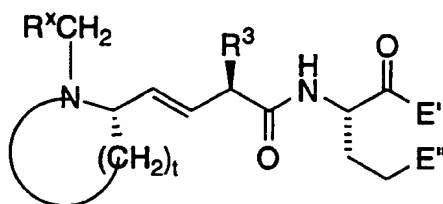
$\text{R}^3\text{MgCuCNCIBF}_3$

Step G

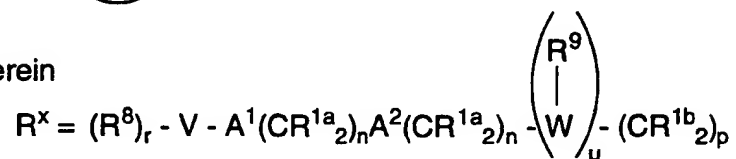


1. HCl
2. NaCNBH_3
 R^xCHO

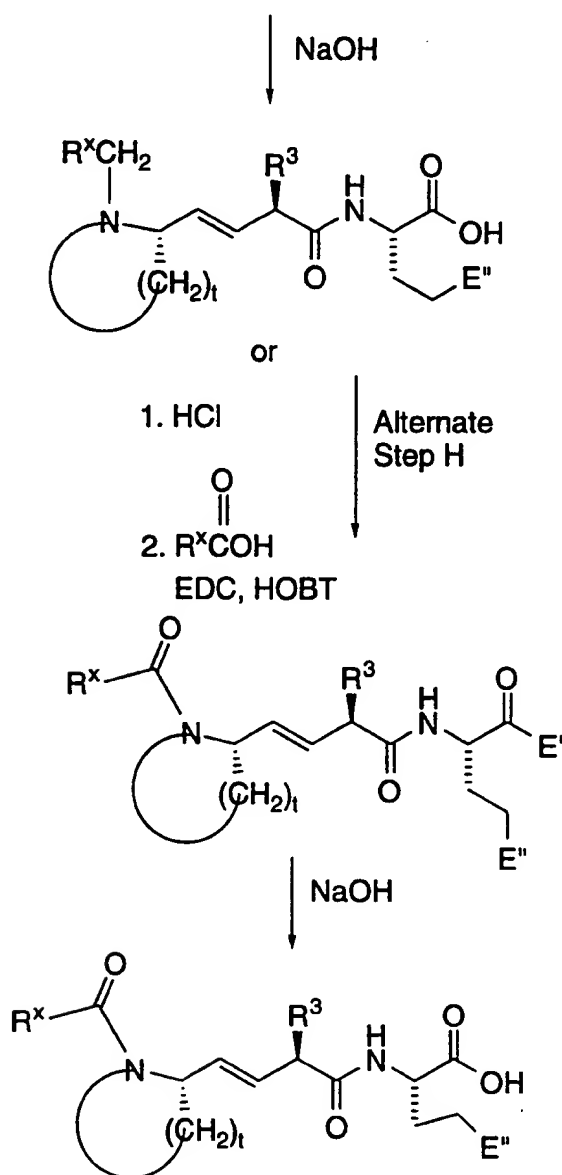
Step H



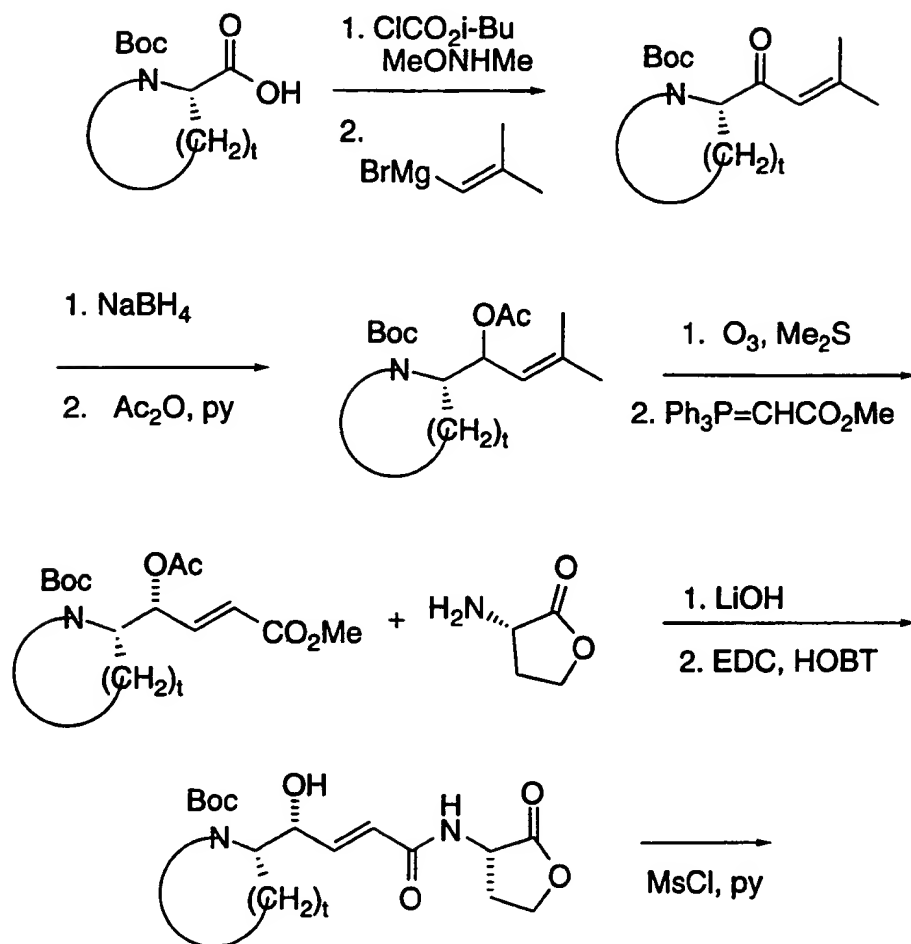
wherein



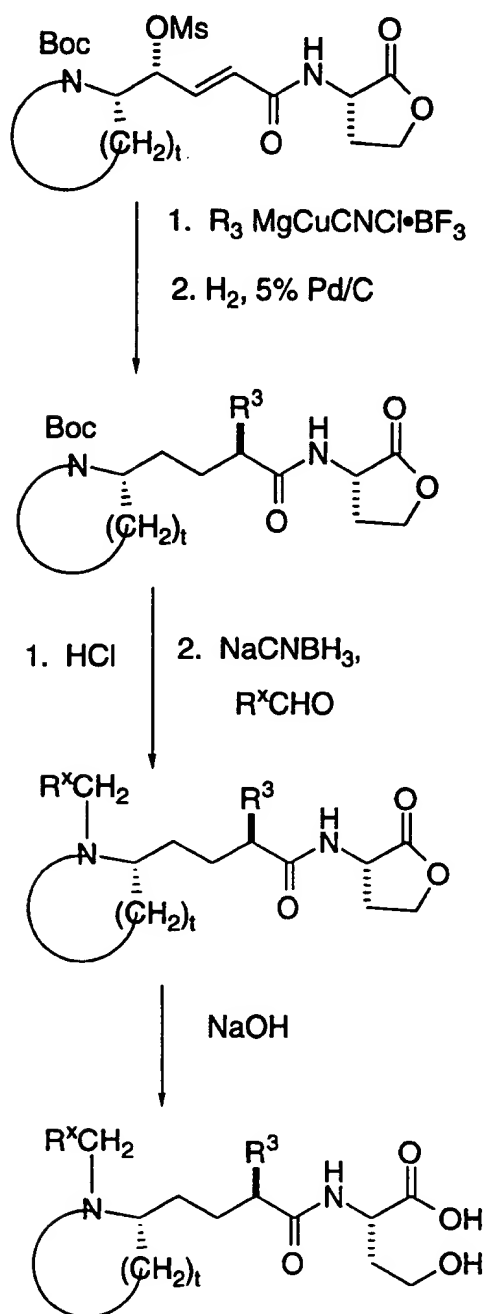
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REACTION SCHEME F (CONT'D)

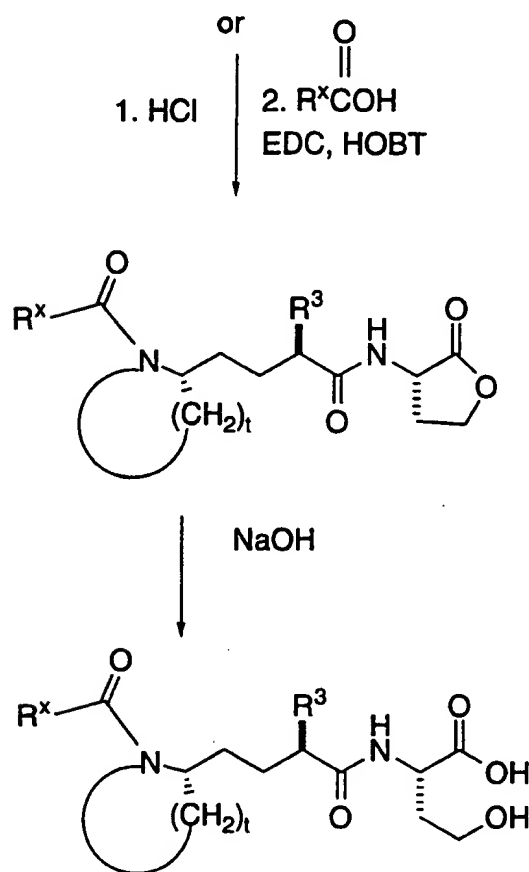
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REACTION SCHEME G

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REACTION SCHEME G (CONT'D)

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REACTION SCHEME G (CONT'D)

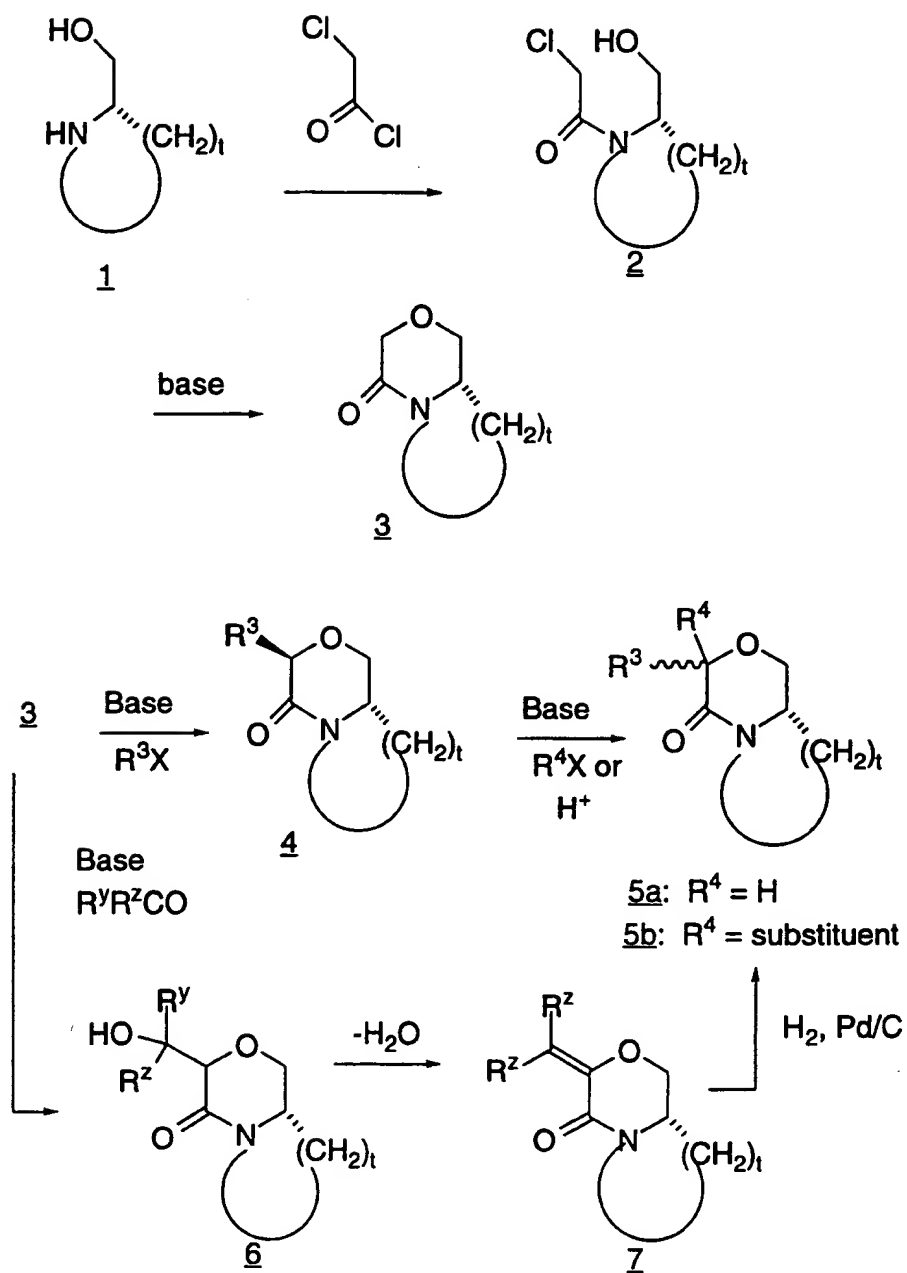
- The oxa isostere compounds of this invention are prepared according to the route outlined in Scheme H. An aminoalcohol 1 is acylated with alpha-chloroacetyl chloride in the presence of trialkylamines to yield amide 2. Subsequent reaction of 2 with a deprotonation reagent (e.g., sodium hydride or potassium t-butoxide) in an ethereal solvent such as THF provides morpholinone 3. Alkylation of 3 with R^3XL , where XL is a leaving group such as Br^- , I^- or Cl^- in THF/DME (1,2-dimethoxyethane) in the presence of a suitable base, preferably NaHMDS [sodium bis(trimethylsilyl)amide], affords 4, which is retreated with NaHMDS followed by either protonation or the addition of an alkyl halide R^4X to give 5a or 5b, respectively, as a enantiomeric mixture. Alternatively, 5a can be prepared from 3 via an

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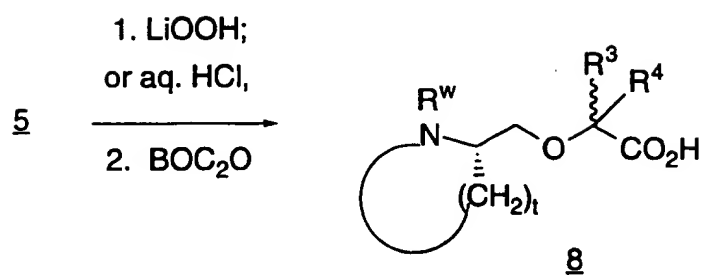
aldol condensation approach. Namely, deprotonation of 3 with NaHMDS followed by the addition of a carbonyl compound RYR^ZCO gives the adduct 6. Dehydration of 6 can be effected by mesylation and subsequent elimination catalyzed by DBU (1,8-diazabicyclo[5.4.0]undec-
5 7-ene) or the direct treatment of 6 with phosphorus oxychloride in pyridine to give olefin 7. Then, catalytic hydrogenation of 7 yields 5a (wherein -CHRYR^Z constitutes R³). Direct hydrolysis of 5 with lithium hydrogen peroxide in aqueous THF, or aqueous HCl, produces acid 8a. Compound 8a is then derivatized with BOC-ON or BOC anhydride to
10 give 8b. The peptide coupling of acid 8b with either an alpha-aminolactone (e.g., homoserine lactone, etc.) or the ester of an amino acid is carried out under the conditions exemplified in the previously described references to yield derivative 9. Treatment of 9 with gaseous hydrogen chloride gives 10, which undergoes further elaboration as
15 described in Reaction Schemes J- hereinbelow.

An alternative method for the preparation of the prolyl oxa isostere (compounds 23 and 24) is shown in Scheme H-1. Referring to Scheme H-1, the aminoalcohol 1 is protected with trifluoroacetic anhydride and the blocked compound 15 treated with diphenyl disulfide
20 in the presence of tributylphosphine to provide the thioether 16. Chlorination of compound 16 provides compound 17 which can be reacted with the appropriate carboxylic acid alcohol in the presence of silver perchlorate and tin (II) chloride, to afford the mixed acetal 18. Removal of the phenylmercapto moiety with Raney nickel provides
25 compound 19. Compound 19 is doubly deprotected, then selectively BOC protected to provide the acid 20, which undergoes the steps previously described for incorporating terminal amino acid. Still another alternative method for the preparation of the prolyl oxa isostere (compounds 23 and 24) is described in the literature [Ruth E.
30 TenBrink, J. Org. Chem., **52**, 418-422 (1987)].

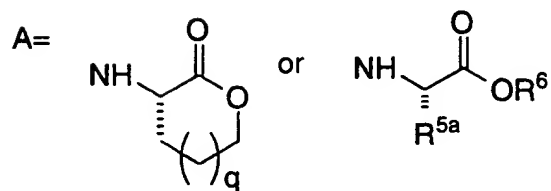
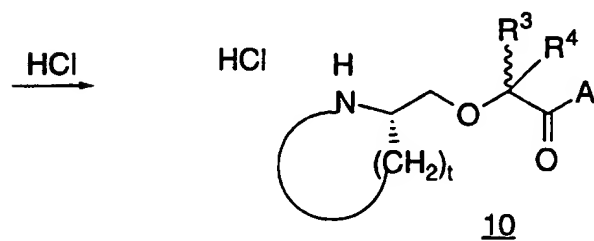
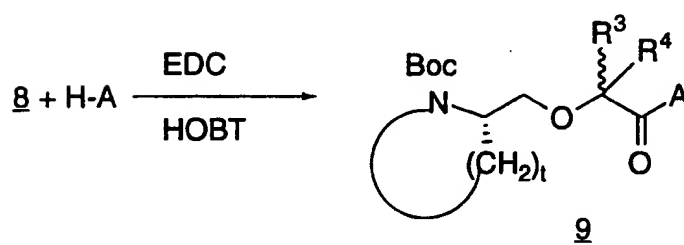
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SCHEME H

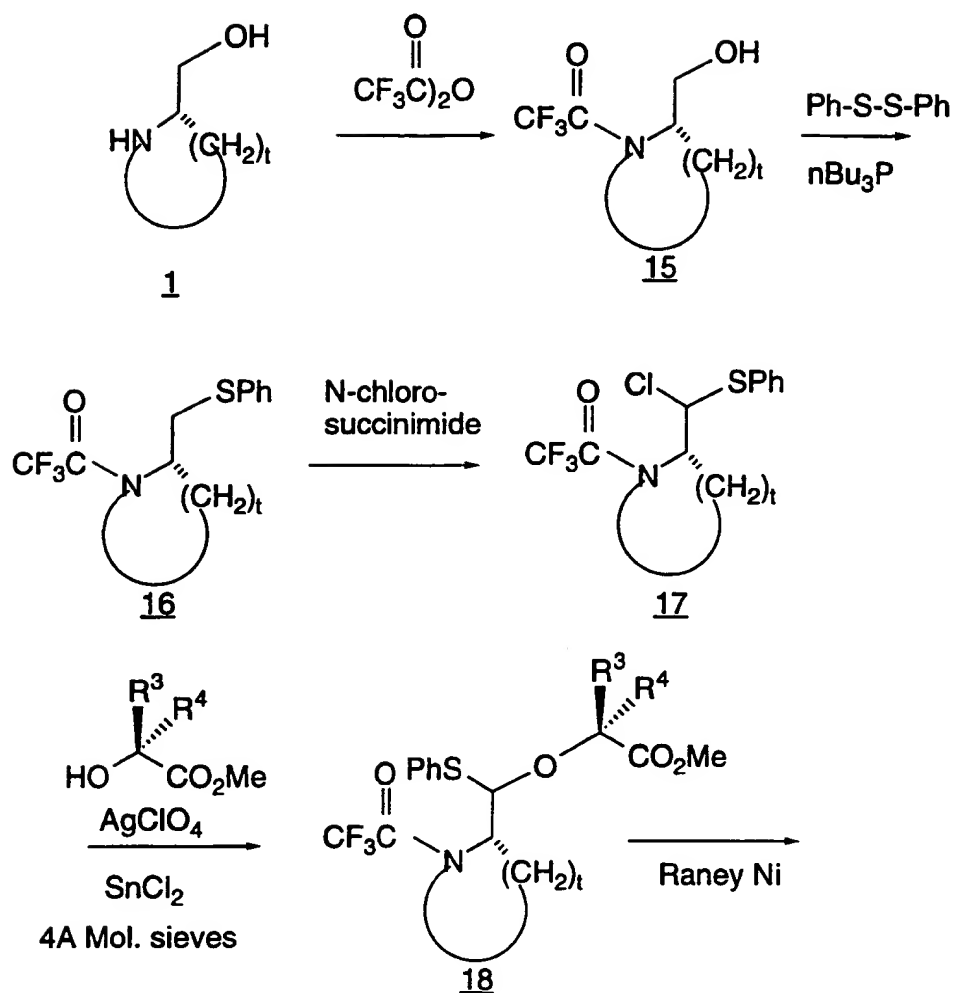
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SCHEME H (CONTD)

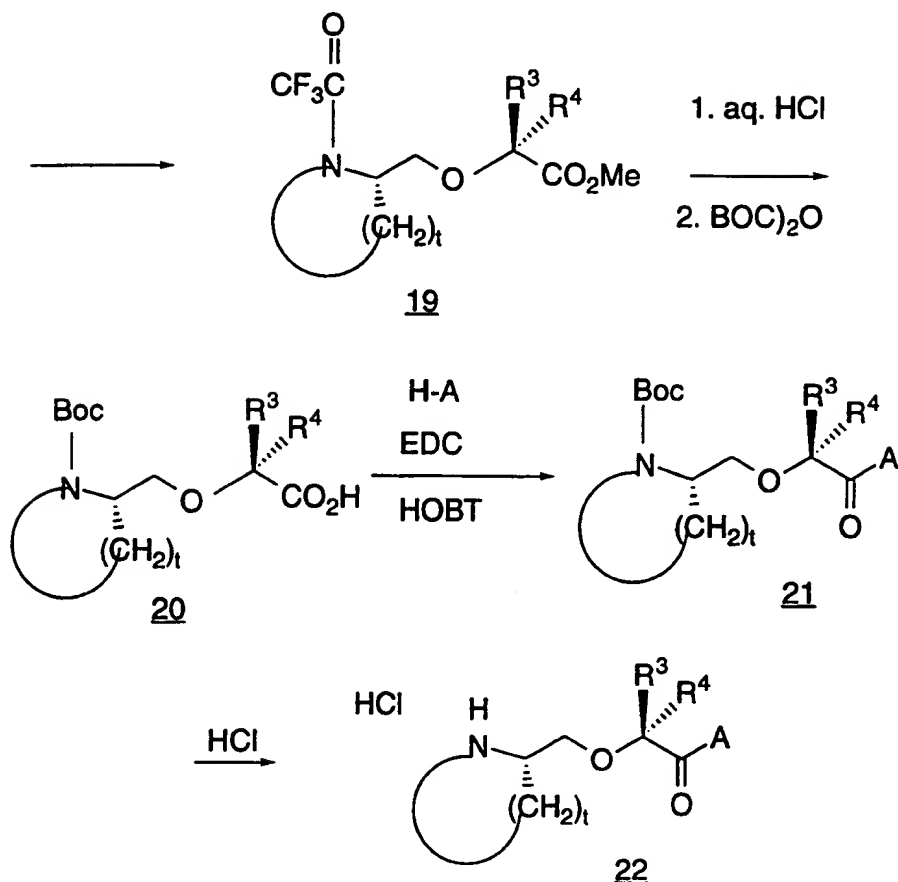
a, $R^w = \text{H}$
 b, $R^w = \text{BOC}$



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SCHEME H-1

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SCHEME H-1 (CONT'D)

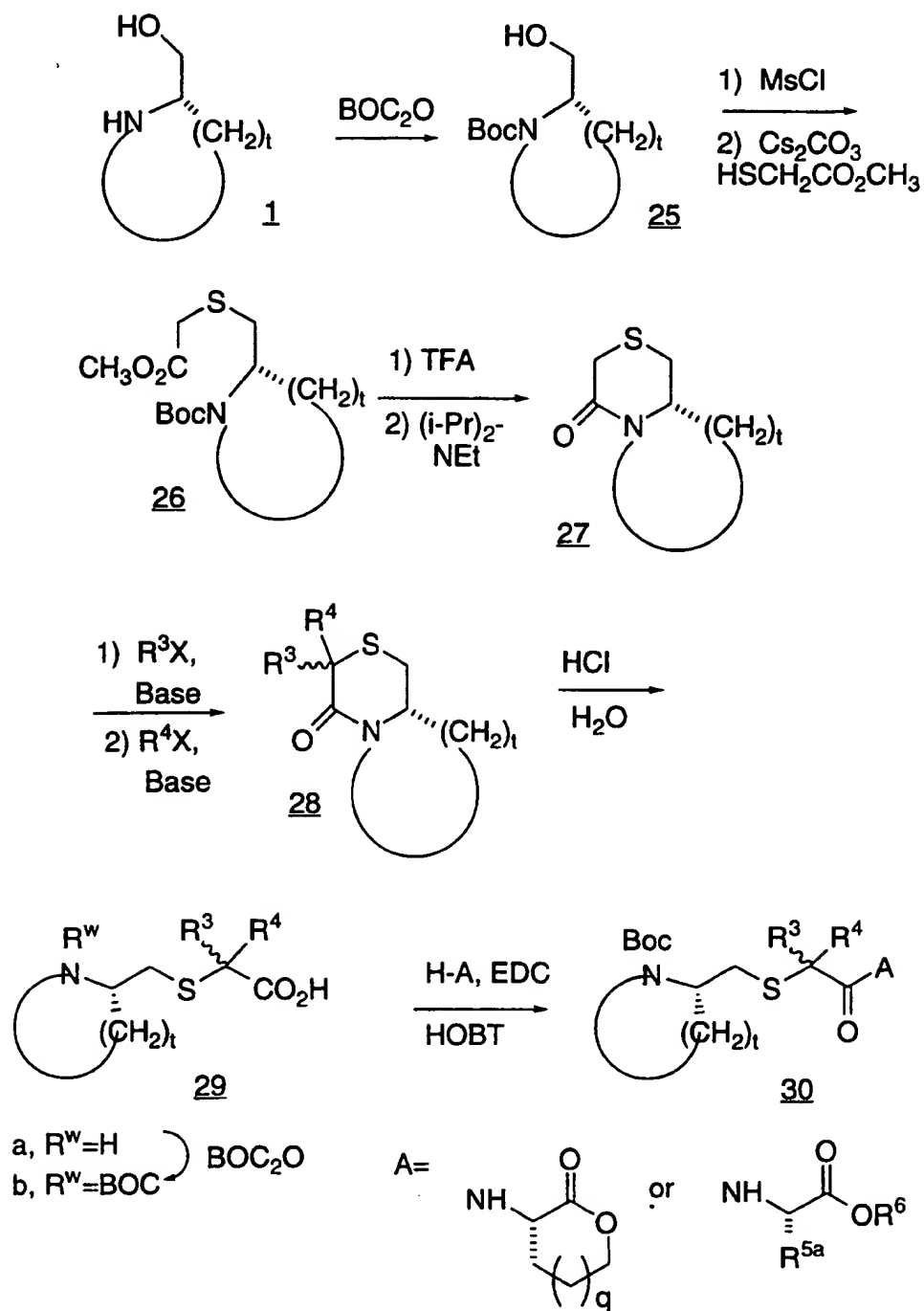
- The thia, oxothia and dioxothia isostere compounds of this invention are prepared in accordance to the route depicted in Scheme I. Aminoalcohol **1** is derivatized with BOC_2O to give **25**. Mesylation of **25** followed by reaction with methyl alpha-mercaptoacetate in the presence of cesium carbonate gives sulfide **26**. Removal of the BOC group in **26** with TFA followed by neutralization with di-isopropylethylamine leads to lactam **27**. Sequential alkylation of **27** with the alkyl halides R^3X and R^4X in THF/DME using NaHDMS as the deprotonation reagent produces **28**. Hydrolysis of **28** in hydro-chloride to yield **29a**, which is derivatized with Boc anhydride to yield **29b**. The coupling of **29b** with an alpha-aminolactone (e.g., homoserine lactone, etc.) or the ester of an amino acid is carried out under conventional

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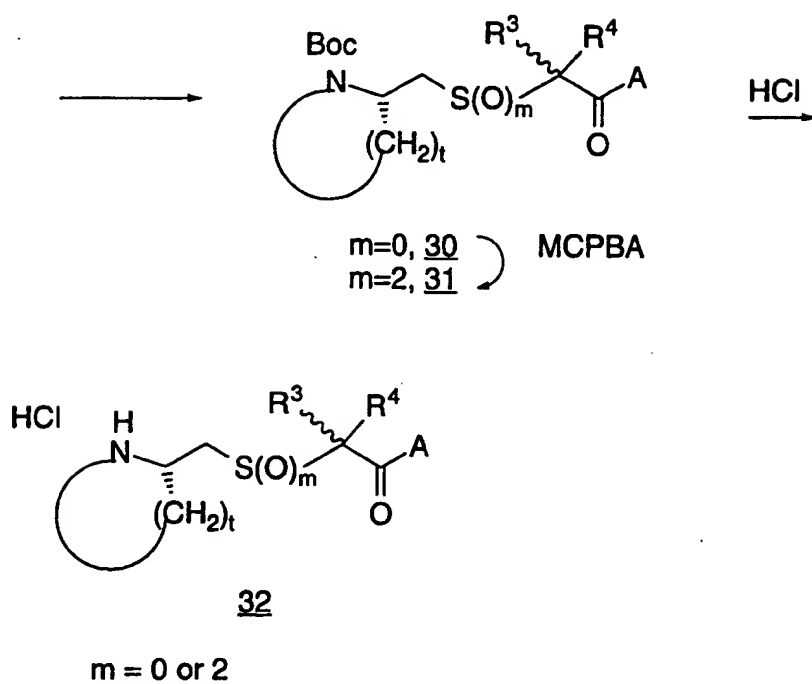
conditions as exemplified in the previously described references to
afford 30. Sulfide 30 is readily oxidized to sulfone 31 by the use of
MCPBA (m-chloroperoxybenzoic acid). The N-BOC group of either
30 or 31 is readily removed by treatment with gaseous hydrogen
5 chloride.

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SCHEME I



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SCHEME I (CONT'D)

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Reaction Schemes J - R illustrate reactions wherein the non-sulfhydryl-containing moiety at the N-terminus of the compounds of the instant invention is attached to the fully elaborated cyclic amino peptide unit, prepared as described in Reaction Schemes A-I. It is understood
5 that the reactions illustrated may also be performed on a simple cyclic amino acid, which may then be further elaborated utilizing reactions described in Reaction Schemes A- I to provide the instant compounds.

The intermediates whose synthesis are illustrated in Reaction Schemes A-I can be reductively alkylated with a variety of
10 aldehydes, such as V, as shown in Reaction Scheme J. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, 1988, 67, 69-75, from the appropriate amino acid (Reaction Scheme F). The reductive alkylation can be accomplished at pH 5-7 with a variety of
15 reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The product VI can be deprotected with trifluoroacetic acid in methylene chloride to give the final compounds VII. The final product VII is isolated in the salt form, for example, as
20 a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine VII can further be selectively protected to obtain VIII, which can subsequently be reductively alkylated with a second aldehyde to obtain IX. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole XI can be
25 accomplished by literature procedures.

Alternatively, the protected cyclic aminopeptidyl intermediate can be reductively alkylated with other aldehydes such as 1-trityl-4-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give products such as XII (Reaction Scheme K). The trityl protecting group
30 can be removed from XII to give XIII, or alternatively, XII can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole XIV. Alternatively, the dipeptidyl analog intermediate can be acylated or sulfonylated by standard techniques.

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The imidazole acetic acid **XV** can be converted to the protected acetate **XVII** by standard procedures, and **XVII** can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester **XVIII**. Hydrolysis and reaction with the protected dipeptidyl analog intermediate in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as **XIX**.

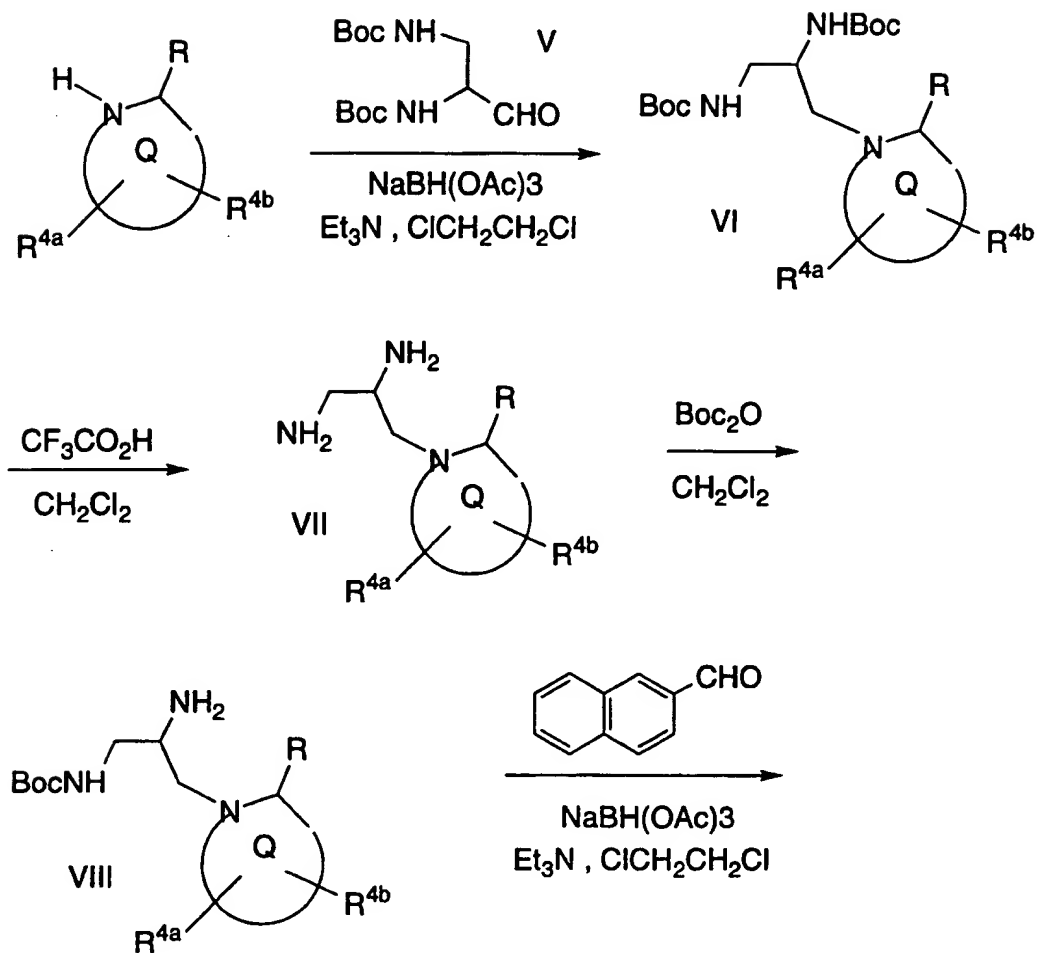
If the protected dipeptidyl analog intermediate is reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as **XX** in Reaction Scheme N, the protecting groups can be subsequently removed to unmask the hydroxyl group (Reaction Schemes N, P). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as **XXIV**. In addition, the fully deprotected amino alcohol **XXV** can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as **XXVI** (Reaction Scheme P), or tertiary amines.

The Boc protected amino alcohol **XXII** can also be utilized to synthesize 2-aziridinylmethylpiperazines such as **XXVII** (Reaction Scheme Q). Treating **XXII** with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine **XXVII**. The aziridine may be reacted in the presence of a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product **XXVIII**.

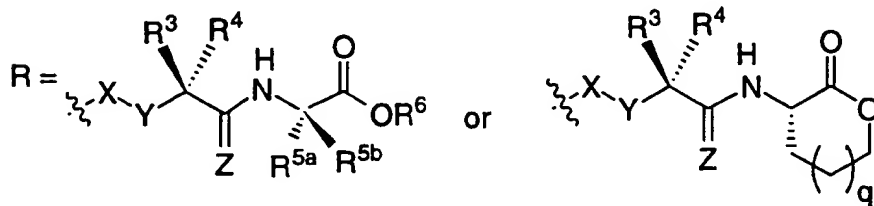
In addition, the protected dipeptidyl analog intermediate can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as **XXXIV**, as shown in Reaction Scheme R. When R' is an aryl group, **XXXIV** can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce **XXXV**. Alternatively, the amine protecting group in **XXXIV** can be removed, and O-alkylated phenolic amines such as **XXXVI** produced.

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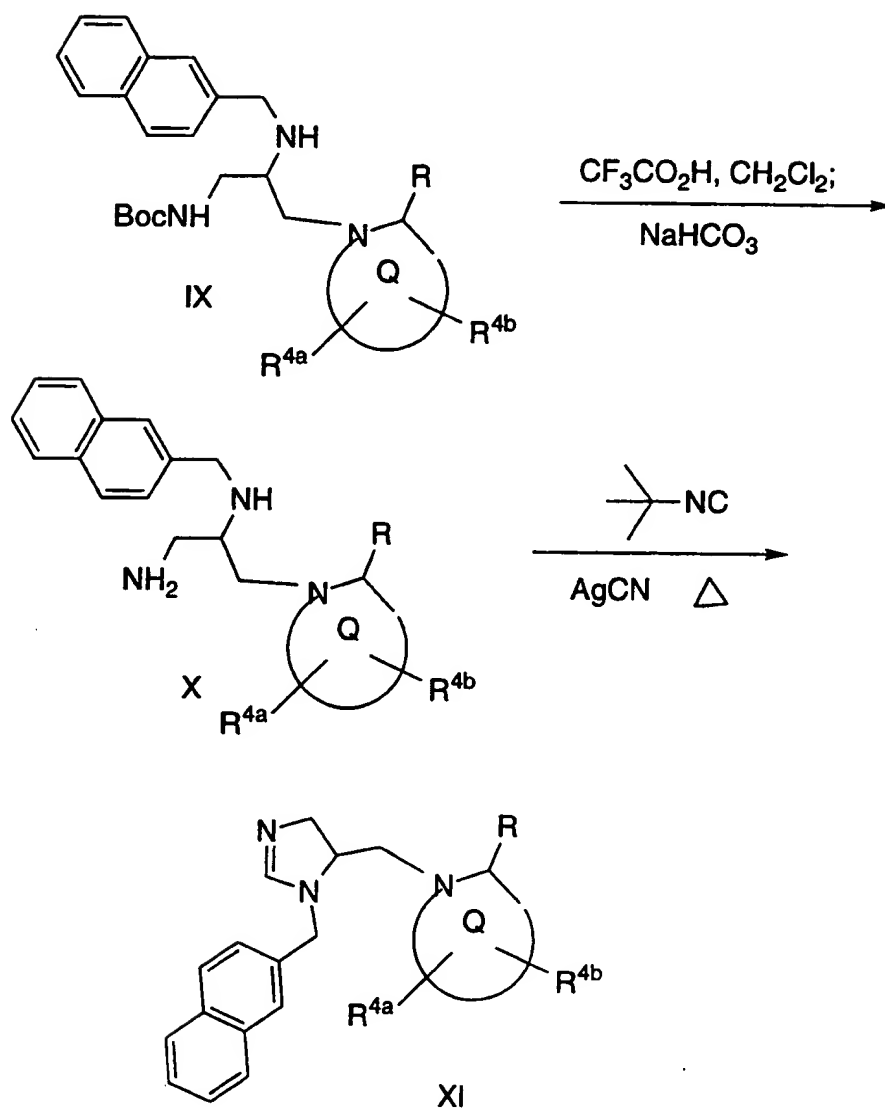
REACTION SCHEME J



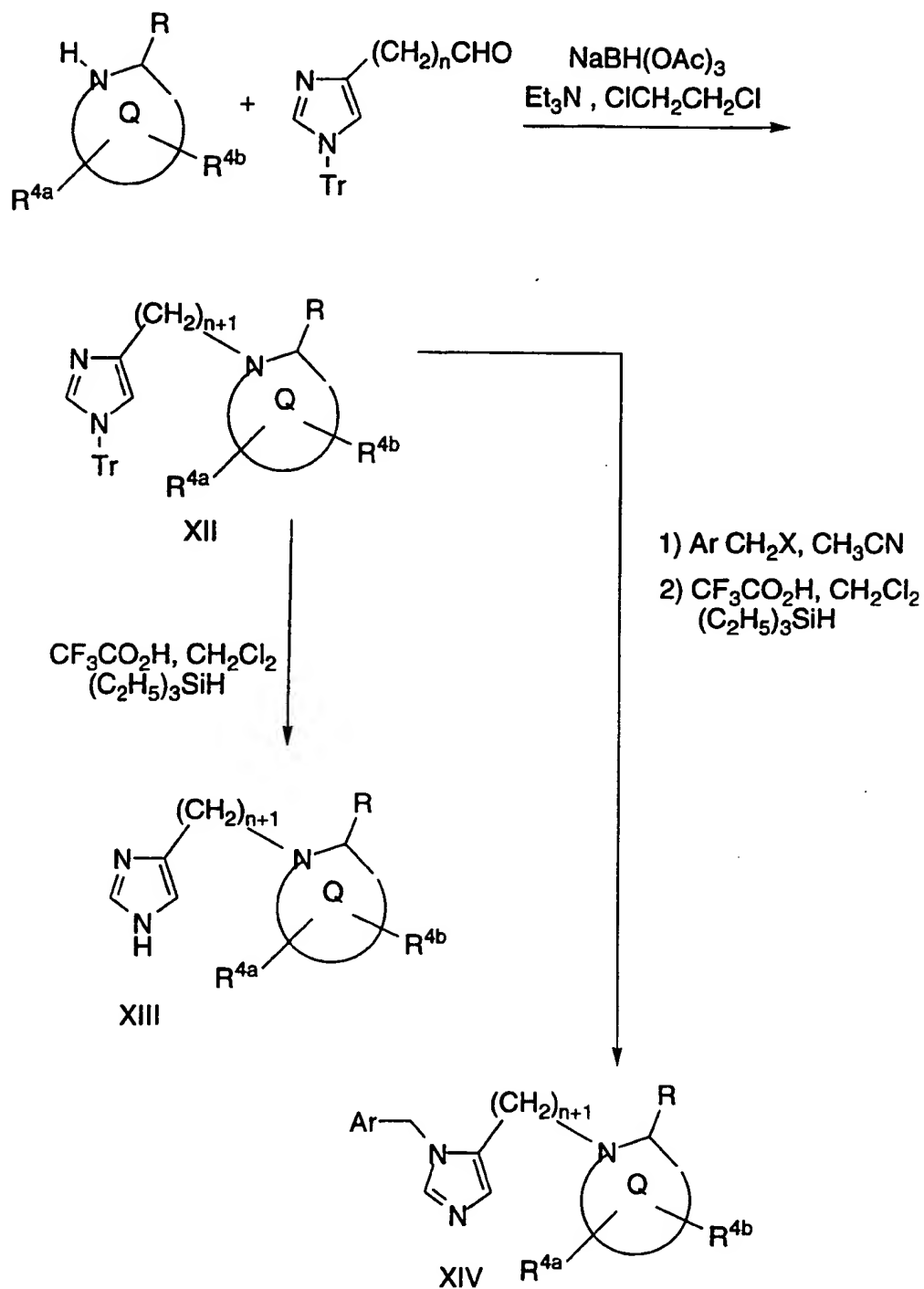
wherein



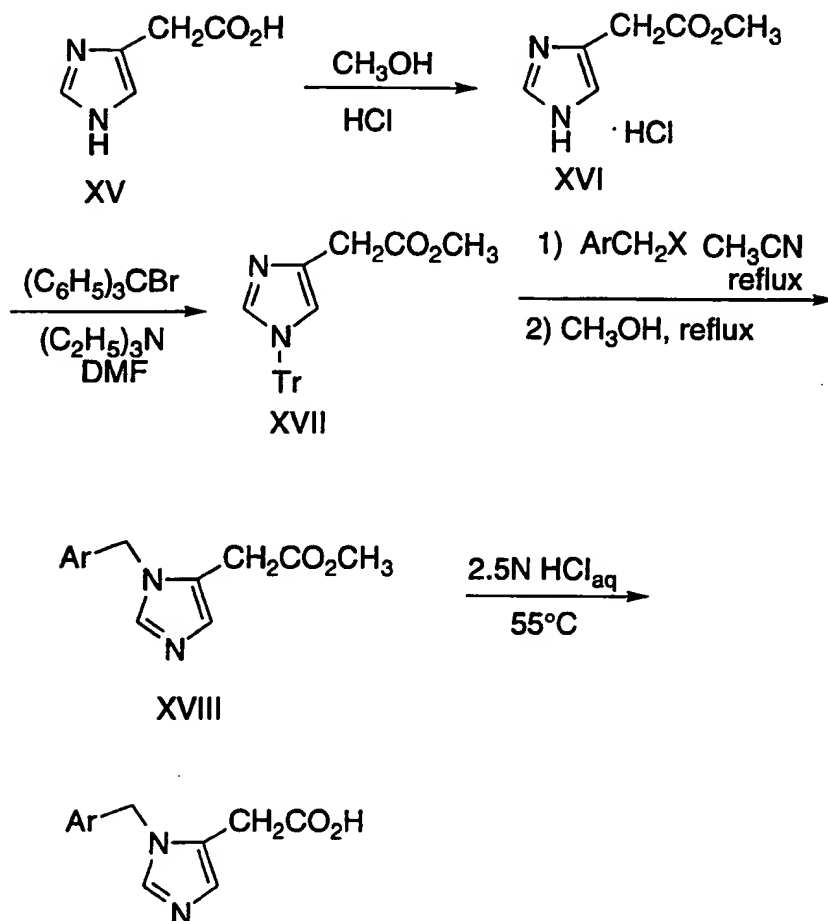
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REACTION SCHEME J (continued)

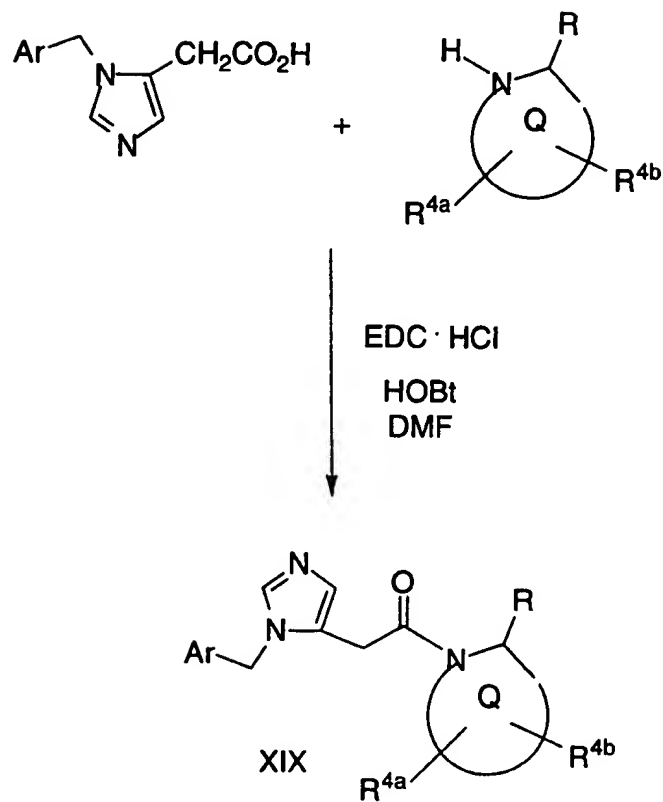
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REACTION SCHEME K

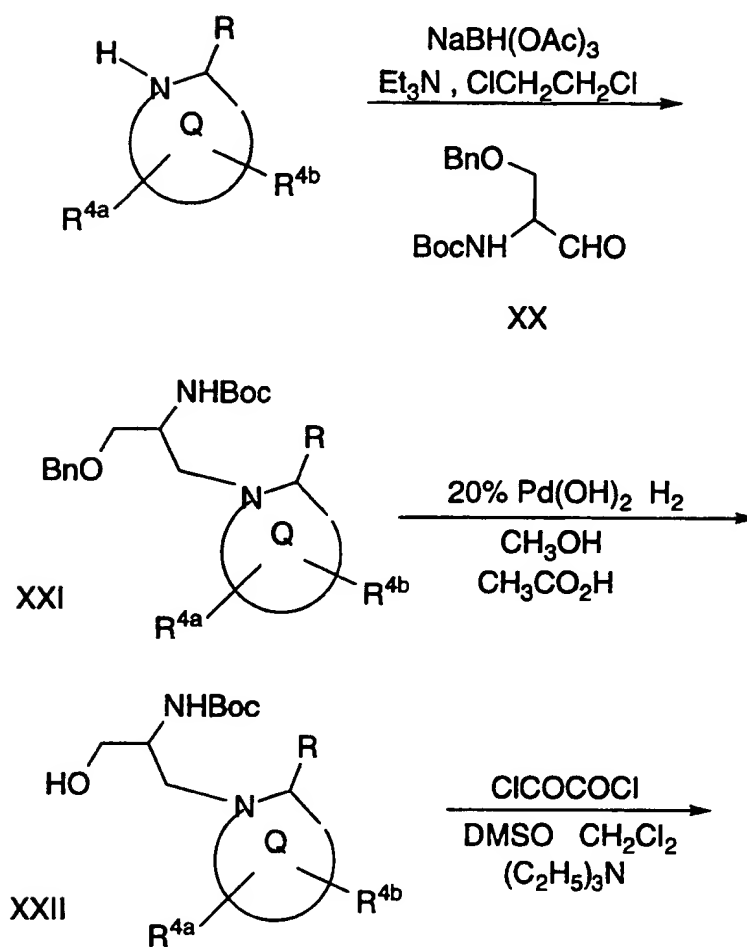
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REACTION SCHEME L

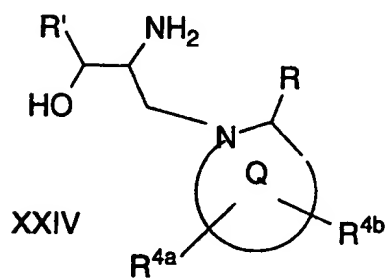
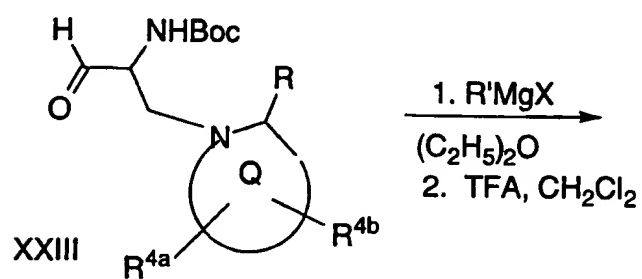
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REACTION SCHEME M

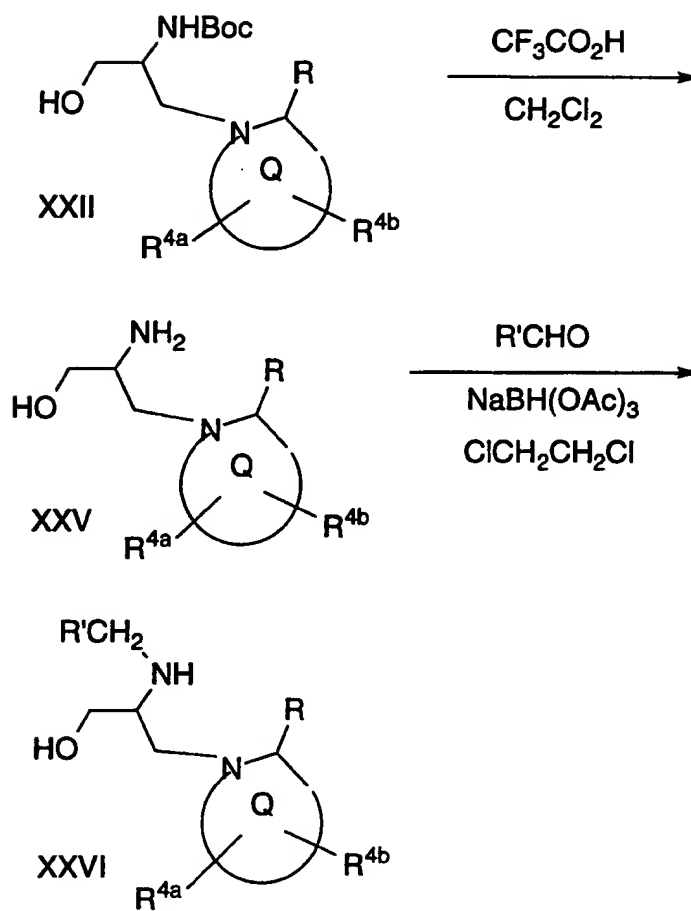
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REACTION SCHEME N

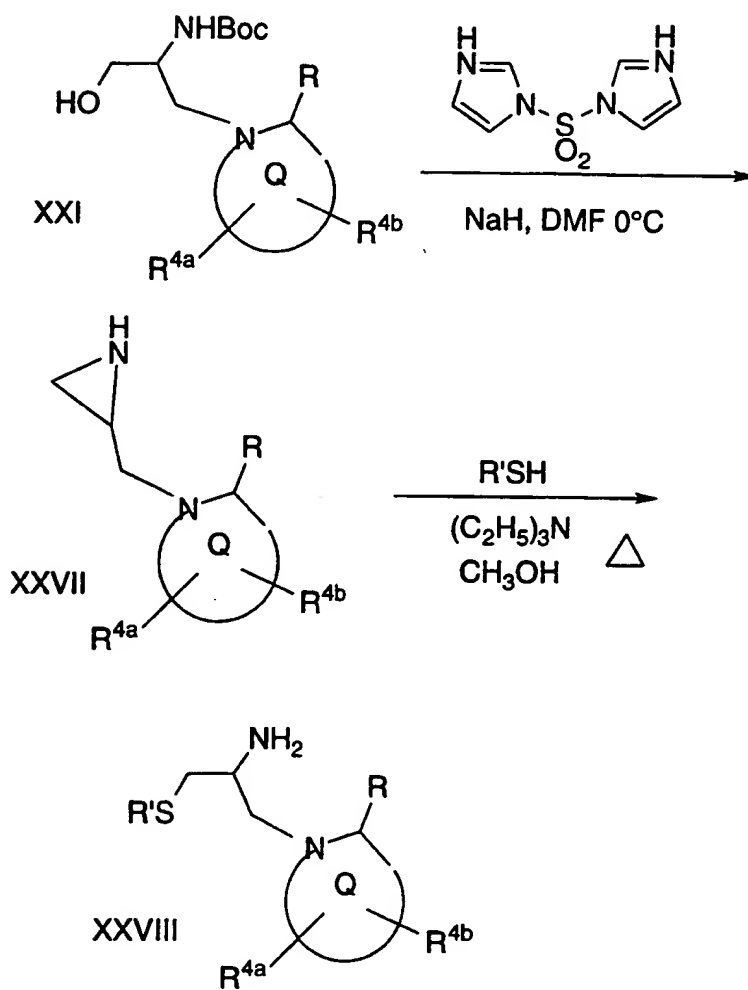
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REACTION SCHEME N (CONTINUED)

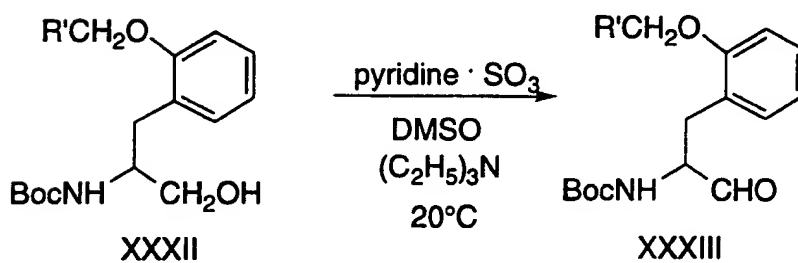
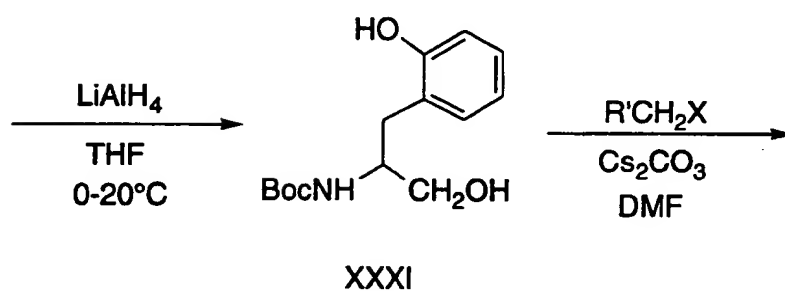
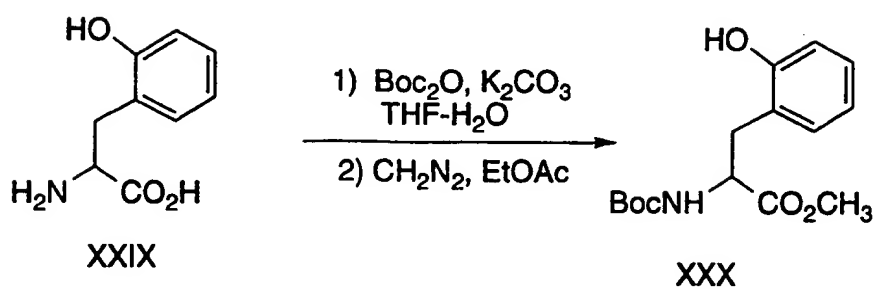
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REACTION SCHEME P

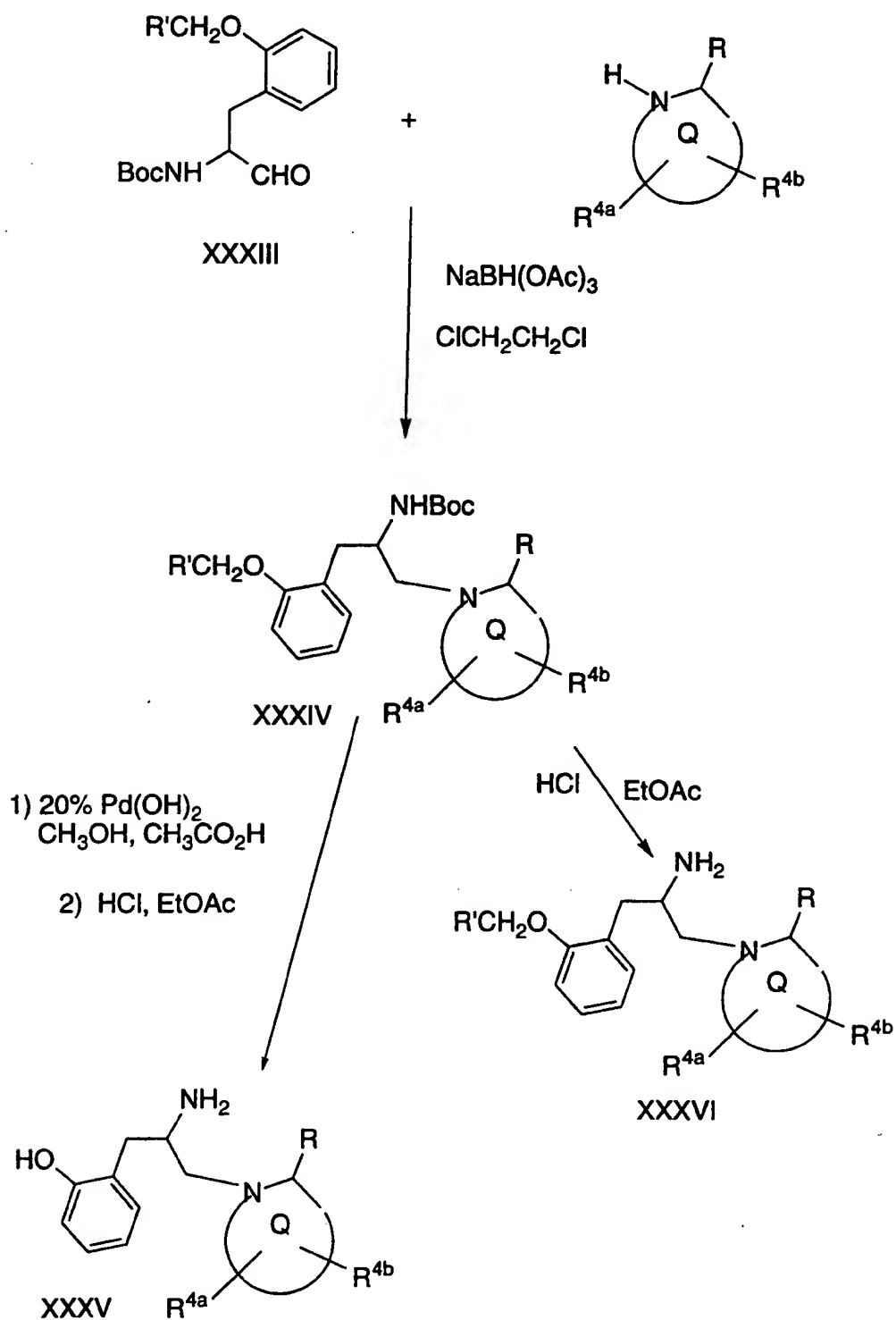
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REACTION SCHEME Q

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REACTION SCHEME R

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REACTION SCHEME R (continued)

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Reactions used to generate the inhibitors of this invention which are designated "y)" are shown in the Reaction Schemes 1-16, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R^a and R^b, as shown in the Schemes, represent the substituents R², R³, R⁴, and R⁵; however their point of attachment to the ring is illustrative only and is not meant to be limiting.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Reaction Schemes. Reaction Schemes 1-16 are also useful in preparing inhibitors of this invention that are designated "1)".

Synopsis of reaction Schemes 1-16:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. In Scheme 1, for example, the synthesis of 2-alkyl substituted piperazines is outlined, and is essentially that described by J. S. Kiely and S. R. Priebe in Organic Preparations and Proceedings Int., 1990, 22, 761-768. Boc-protected amino acids I, available commercially or by procedures known to those skilled in the art, can be coupled to N-benzyl amino acid esters using a variety of dehydrating agents such as DCC (dicyclohexycarbodiimide) or EDC·HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) in a solvent such as methylene chloride, chloroform, dichloroethane, or in dimethylformamide. The product II is then deprotected with acid, for example hydrogen chloride in chloroform or ethyl acetate, or trifluoroacetic acid in methylene chloride, and cyclized under weakly basic conditions to give the diketopiperazine III. Reduction of III with lithium aluminum hydride in refluxing ether gives the piperazine IV, which is protected as the Boc derivative V. The N-benzyl group can be

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cleaved under standard conditions of hydrogenation, e.g., 10% palladium on carbon at 60 psi hydrogen on a Parr apparatus for 24-48 h. The product VI can be treated with an acid chloride, or a carboxylic acid under standard dehydrating conditions to furnish the carboxamides VII; a final acid deprotection as previously described gives the intermediate VIII (Scheme 2). The intermediate VIII can be reductively alkylated with a variety of aldehydes, such as IX. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, 1988, 67, 69-75, from the appropriate amino acid (Scheme 3). The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The product X can be deprotected to give the final compounds XI with trifluoroacetic acid in methylene chloride. The final product XI is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine XI can further be selectively protected to obtain XII, which can subsequently be reductively alkylated with a second aldehyde to obtain XIII. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole XV can be accomplished by literature procedures.

Alternatively, the protected piperazine intermediate VII can be reductively alkylated with other aldehydes such as 1-trityl-4-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give products such as XVI (Scheme IV). The trityl protecting group can be removed from XVI to give XVII, or alternatively, XVI can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole XVIII. Alternatively, the intermediate VIII can be acylated or sulfonylated by standard techniques. The imidazole acetic acid XIX can be converted to the acetate XXI by standard procedures, and XXI can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester XXII. Hydrolysis and reaction with piperazine VIII in the

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presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as XXIV.

If the piperazine VIII is reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as XXV in Scheme 6, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 6, 7). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as XXIX. In addition, the fully deprotected amino alcohol XXX can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXXI (Scheme 7), or tertiary amines.

The Boc protected amino alcohol XXVII can also be utilized to synthesize 2-aziridinylmethylpiperazines such as XXXII (Scheme 8). Treating XXVII with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine XXXII. The aziridine reacted in the presence of a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product XXXIII.

In addition, the piperazine VIII can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as XXXIX. When R' is an aryl group, XXXIX can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XL. Alternatively, the amine protecting group in XXXIX can be removed, and O-alkylated phenolic amines such as XLI produced.

Depending on the identity of the amino acid I, various side chains can be incorporated into the piperazine. For example when I is the Boc-protected β -benzyl ester of aspartic acid, the intermediate diketopiperazine XLII where $n=1$ and $R=\text{benzyl}$ is obtained, as shown in Scheme 10. Subsequent lithium aluminum hydride reduction reduces the ester to the alcohol XLIII, which can then be reacted with a variety of alkylating agents such as an alkyl iodide, under basic conditions, for example, sodium hydride in dimethylformamide or tetrahydrofuran.

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The resulting ether XLIV can then be carried on to final products as described in Schemes 3-9.

N-Aryl piperazines can be prepared as described in Scheme 11. An aryl amine XLV is reacted with *bis* -chloroethyl amine hydrochloride (XLVI) in refluxing *n* -butanol to furnish compounds XLVII. The resulting piperazines XLVII can then be carried on to final products as described in Schemes 3-9.

Piperazin-5-ones can be prepared as shown in Scheme 12. Reductive amination of Boc-protected amino aldehydes XLIX (prepared from I as described previously) gives rise to compound L. This is then reacted with bromoacetyl bromide under Schotten-Baumann conditions; ring closure is effected with a base such as sodium hydride in a polar aprotic solvent such as dimethylformamide to give LI. The carbamate protecting group is removed under acidic conditions such as trifluoroacetic acid in methylene chloride, or hydrogen chloride gas in methanol or ethyl acetate, and the resulting piperazine can then be carried on to final products as described in Schemes 3-9.

The isomeric piperazin-3-ones can be prepared as described in Scheme 13. The imine formed from arylcarboxamides LII and 2-aminoglycinal diethyl acetal (LIII) can be reduced under a variety of conditions, including sodium triacetoxyborohydride in dichloroethane, to give the amine LIV. Amino acids I can be coupled to amines LIV under standard conditions, and the resulting amide LV when treated with aqueous acid in tetrahydrofuran can cyclize to the unsaturated LVI. Catalytic hydrogenation under standard conditions gives the requisite intermediate LVII, which is elaborated to final products as described in Schemes 3-9.

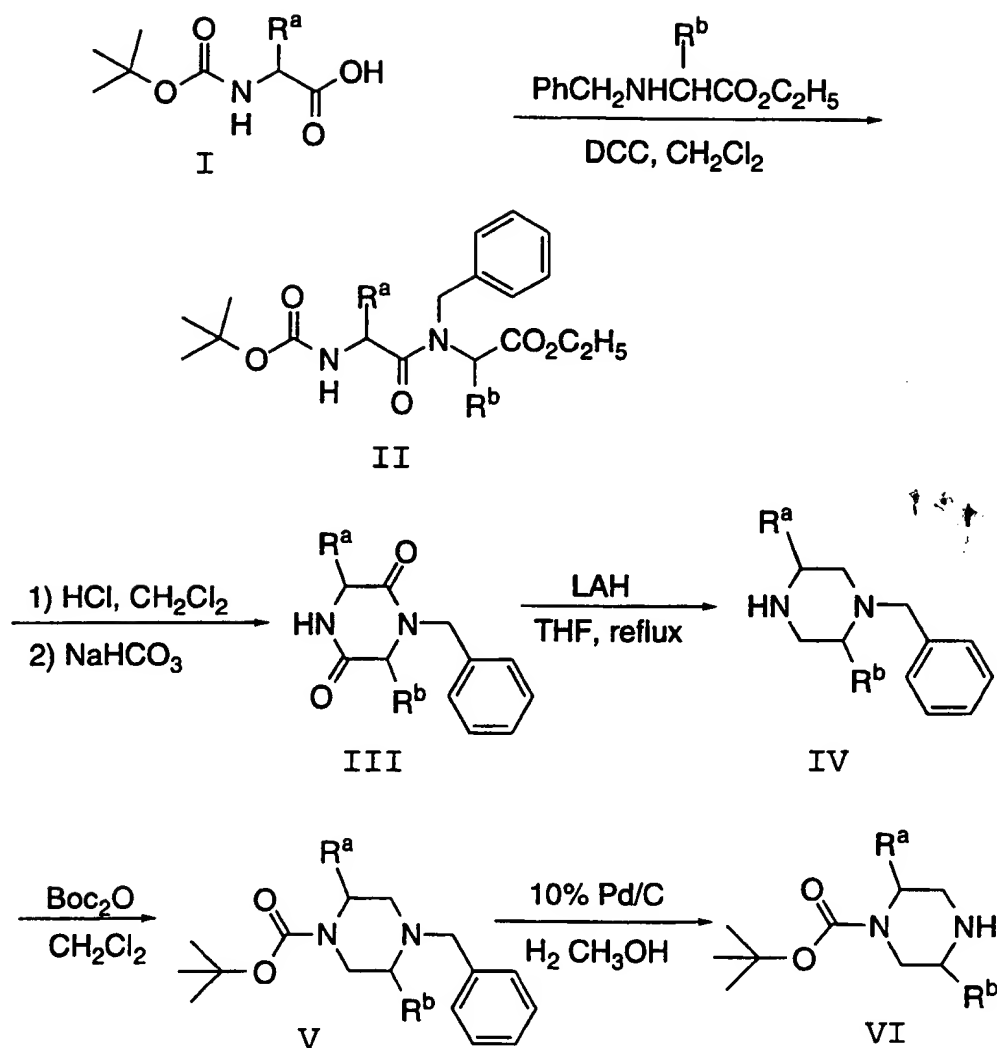
Access to alternatively substituted piperazines is described in Scheme 14. Following deprotection with trifluoroacetic acid, the N-benzyl piperazine V can be acylated with an aryl carboxylic acid. The resulting N-benzyl aryl carboxamide LIX can be hydrogenated in the presence of a catalyst to give the piperazine carboxamide LX which can then be carried on to final products as described in Schemes 3-9.

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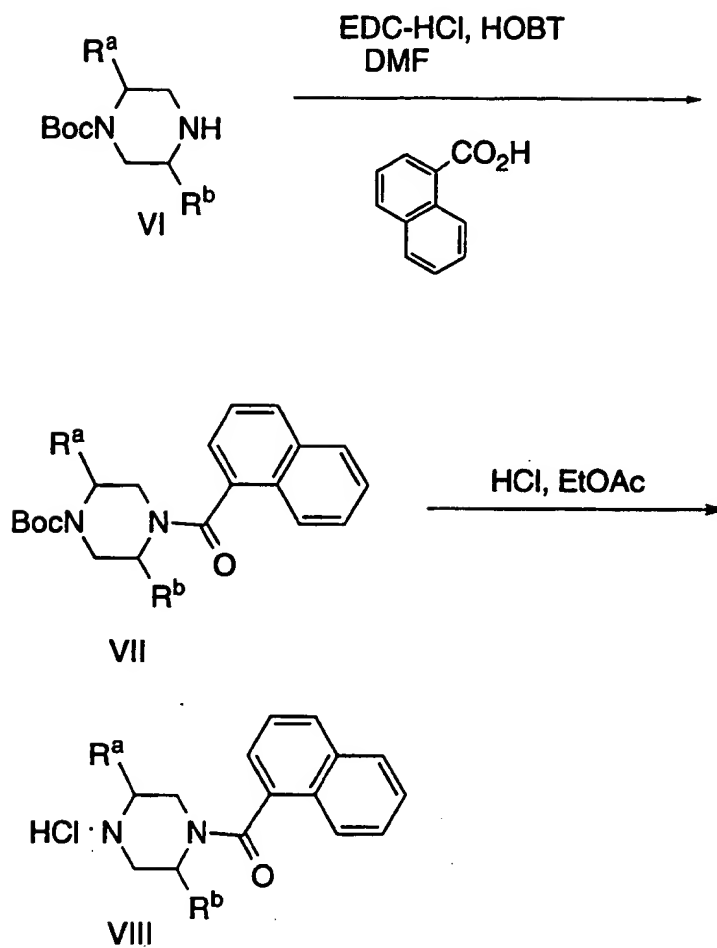
Reaction Scheme 15 provides an illustrative example the synthesis of compounds of the instant invention wherein the substituents R^2 and R^3 are combined to form $-(CH_2)_u-$. For example, 1-aminocyclohexane-1-carboxylic acid LXI can be converted to the
5 spiropiperazine LXVI essentially according to the procedures outlined in Schemes 1 and 2. The piperazine intermediate LXIX can be deprotected as before, and carried on to final products as described in Schemes 3-9. It is understood that reagents utilized to provide the substituent Y which is 2-(naphthyl) and the imidazolylalkyl substituent
10 may be readily replaced by other reagents well known in the art and readily available to provide other N-substituents on the piperazine.

The aldehyde XLIX from Scheme 12 can also be reductively alkylated with an aniline as shown in Scheme 16. The product LXXI can be converted to a piperazinone by acylation with
15 chloroacetyl chloride to give LXXII, followed by base-induced cyclization to LXXIII. Deprotection, followed by reductive alkylation with a protected imidazole carboxaldehyde leads to LXXV, which can be alkylation with an arylmethylhalide to give the imidazolium salt LXXVI. Final removal of protecting groups by either solvolysis with a
20 lower alkyl alcohol, such as methanol, or treatment with triethylsilane in methylene chloride in the presence of trifluoroacetic acid gives the final product LXXVII.

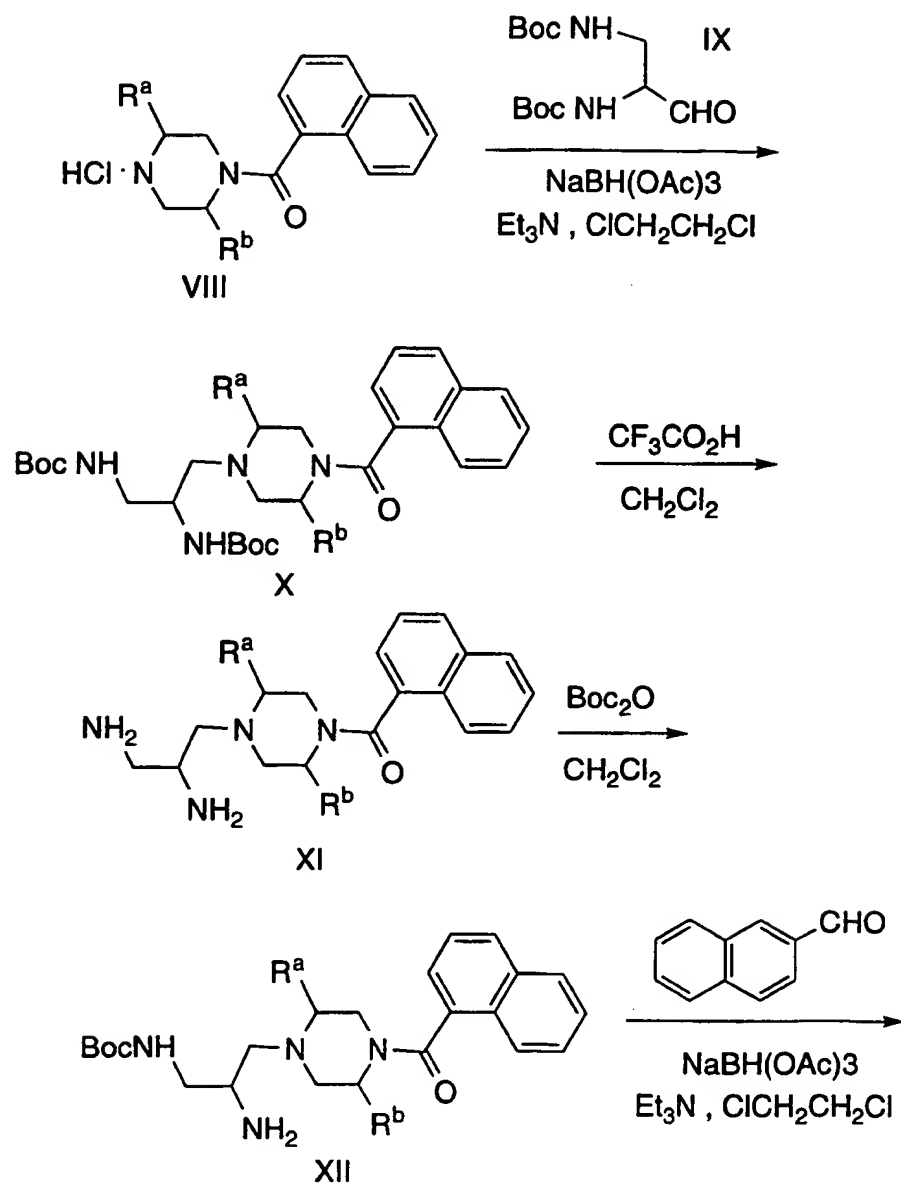
- 195 -

SCHEME 1

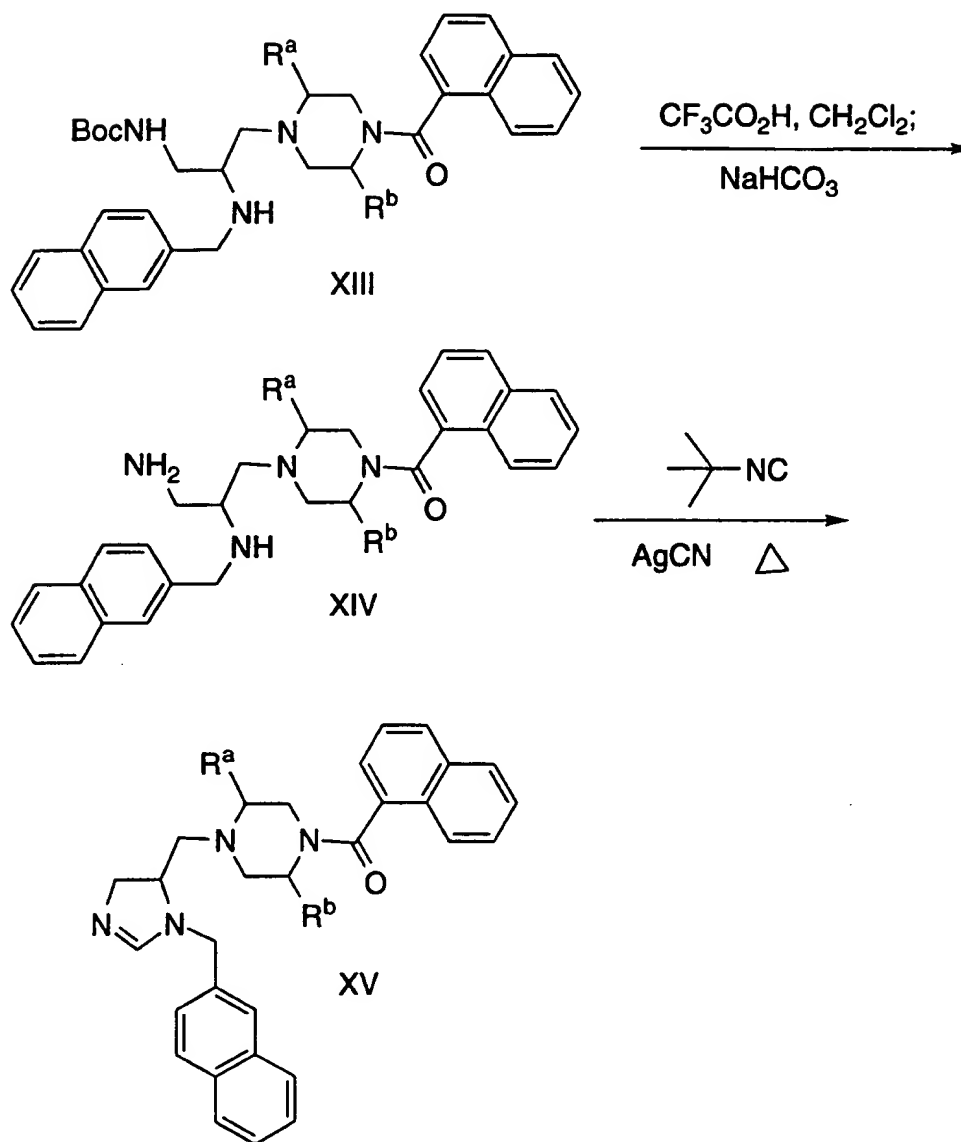
- 196 -

SCHEME 2

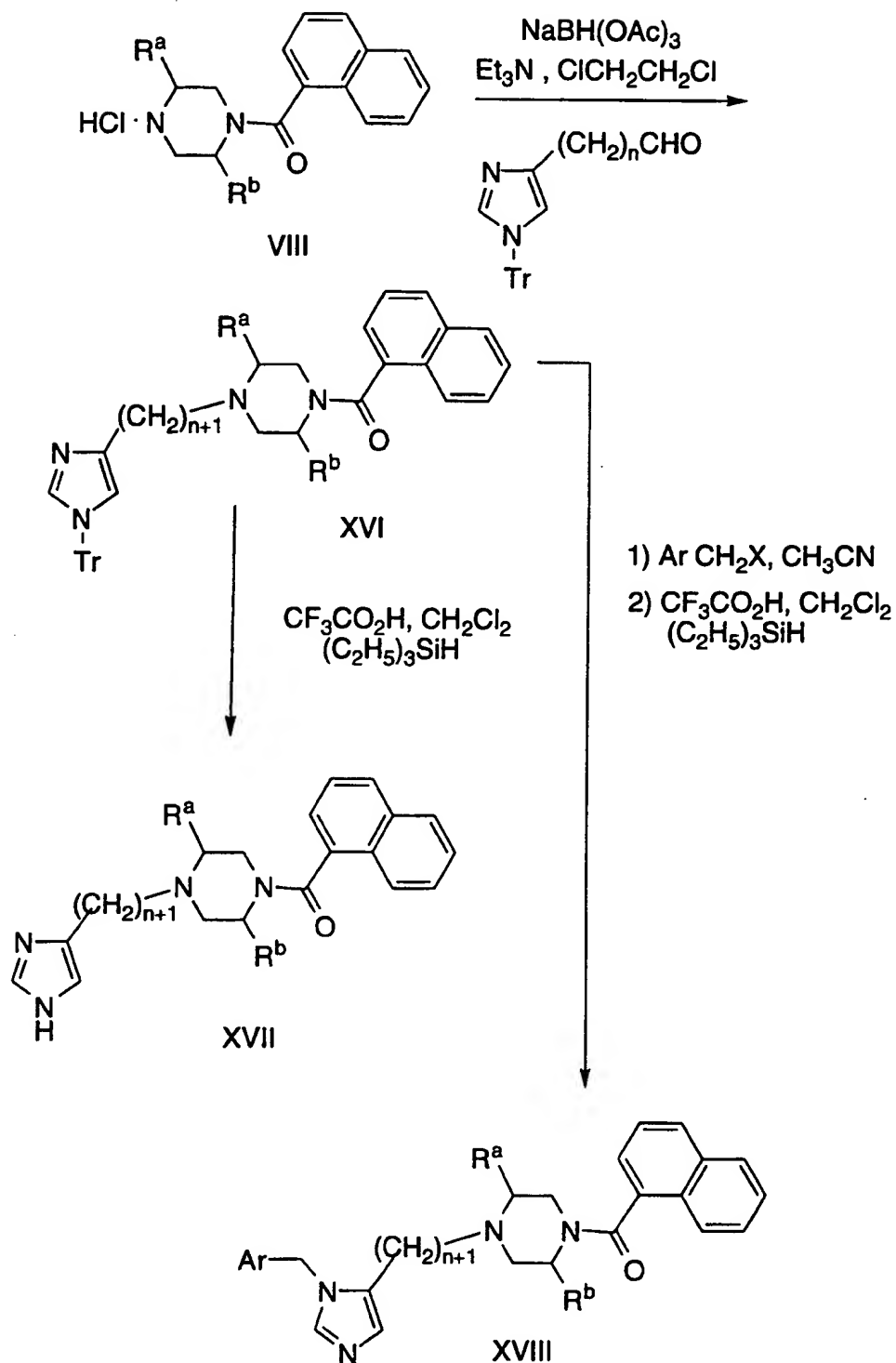
- 197 -

SCHEME 3

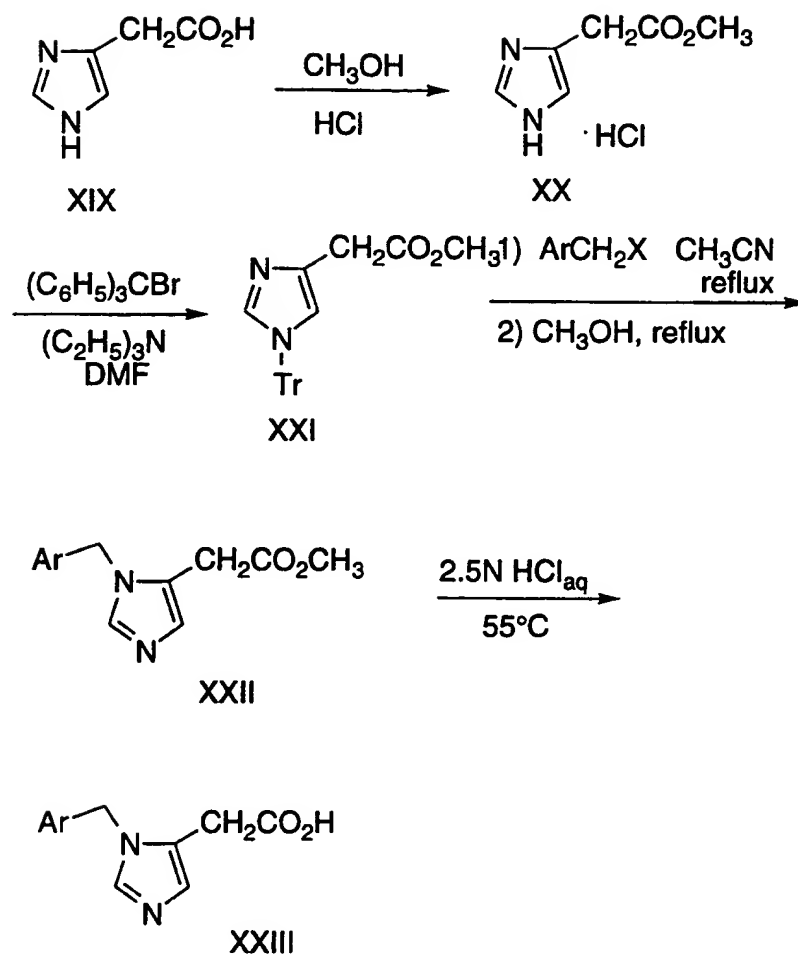
- 198 -

SCHEME 3 (continued)

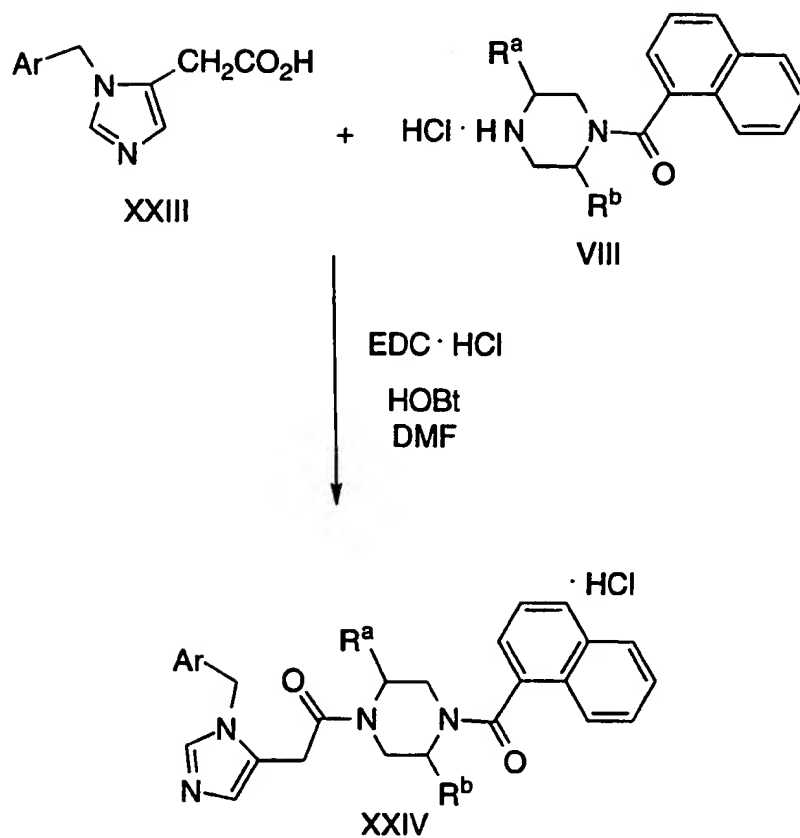
- 199 -

SCHEME 4

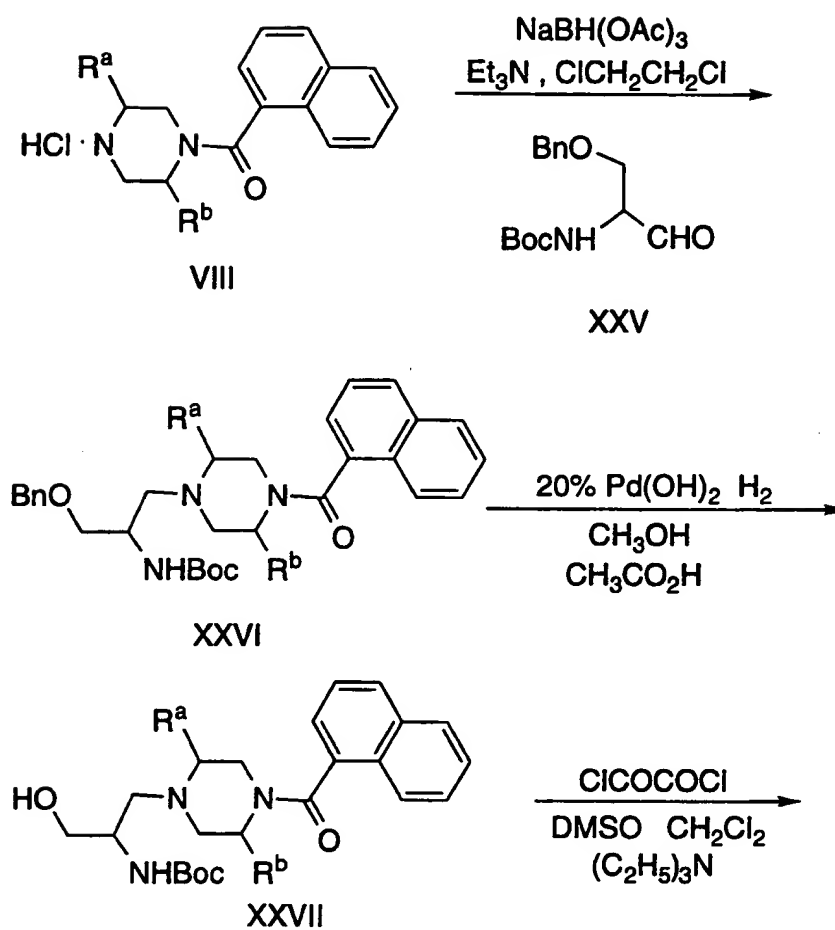
- 200 -

SCHEME 5

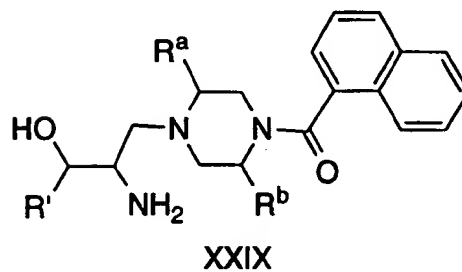
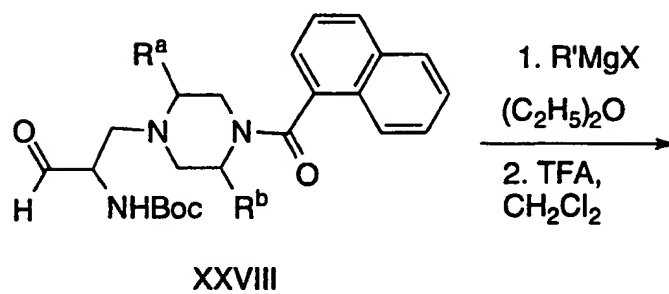
- 201 -

SCHEME 5 (continued)

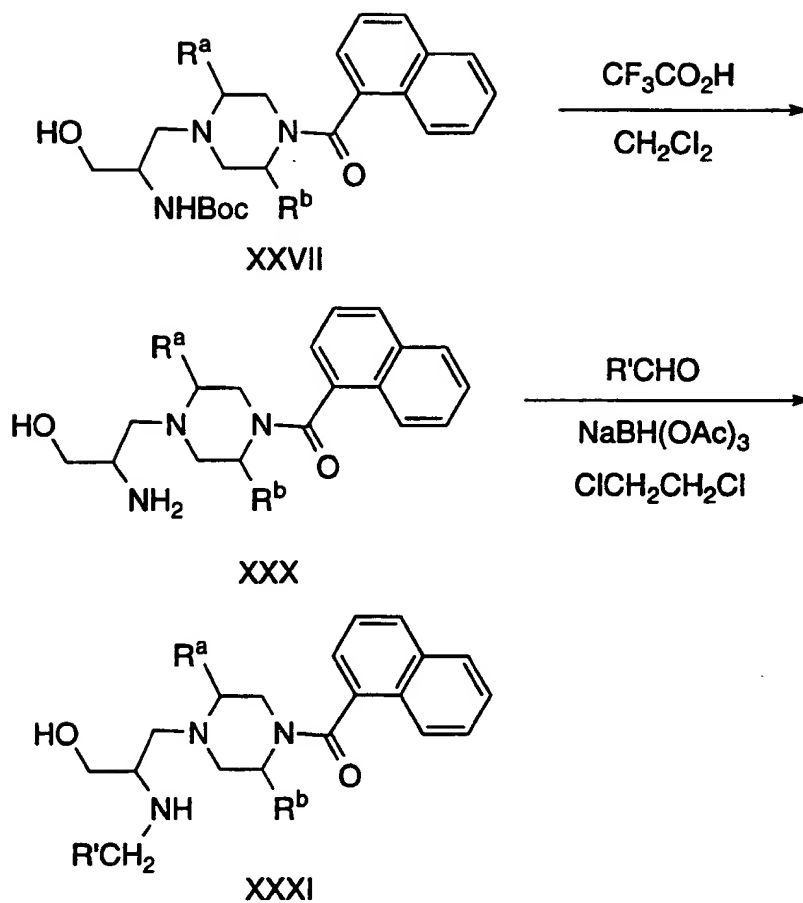
- 202 -

SCHEME 6

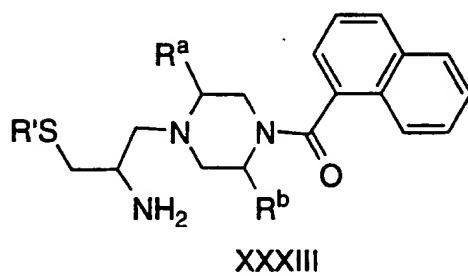
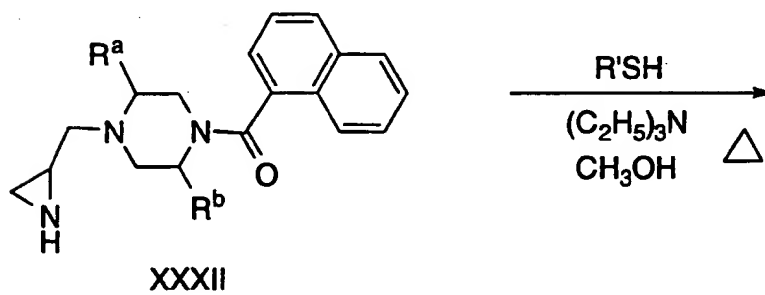
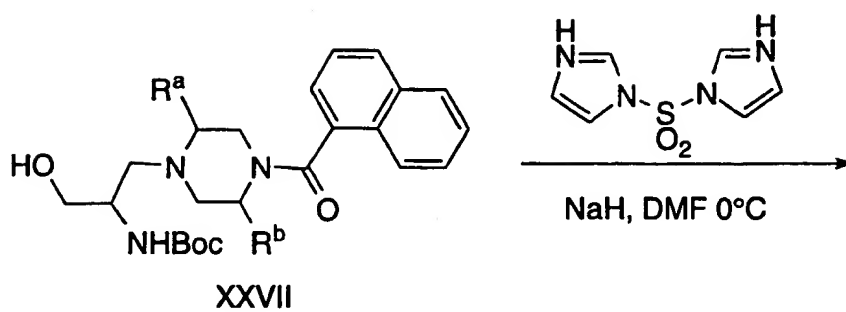
- 203 -

SCHEME 6 (CONTINUED)

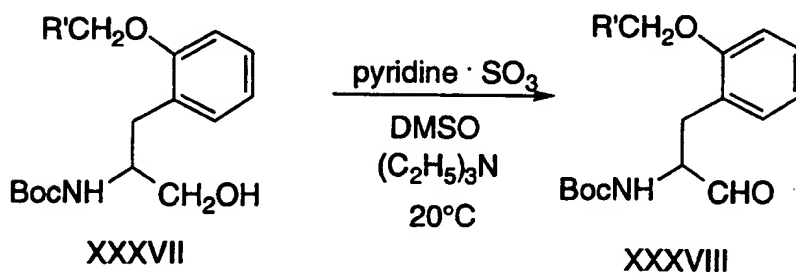
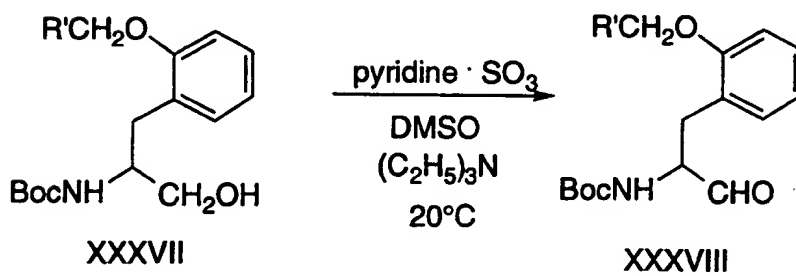
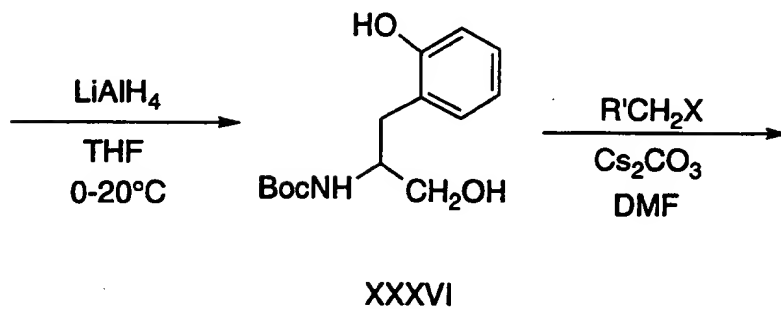
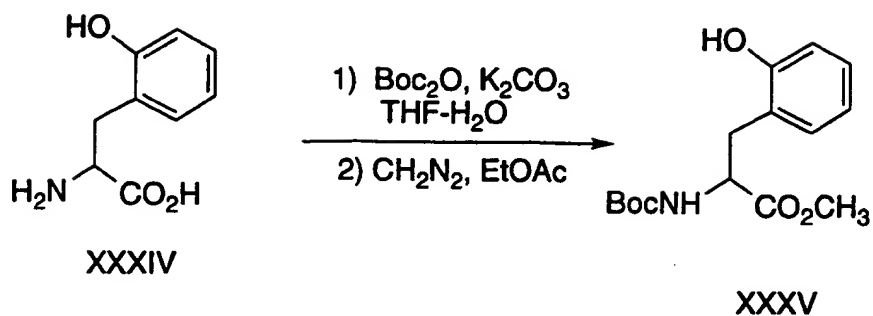
- 204 -

SCHEME 7

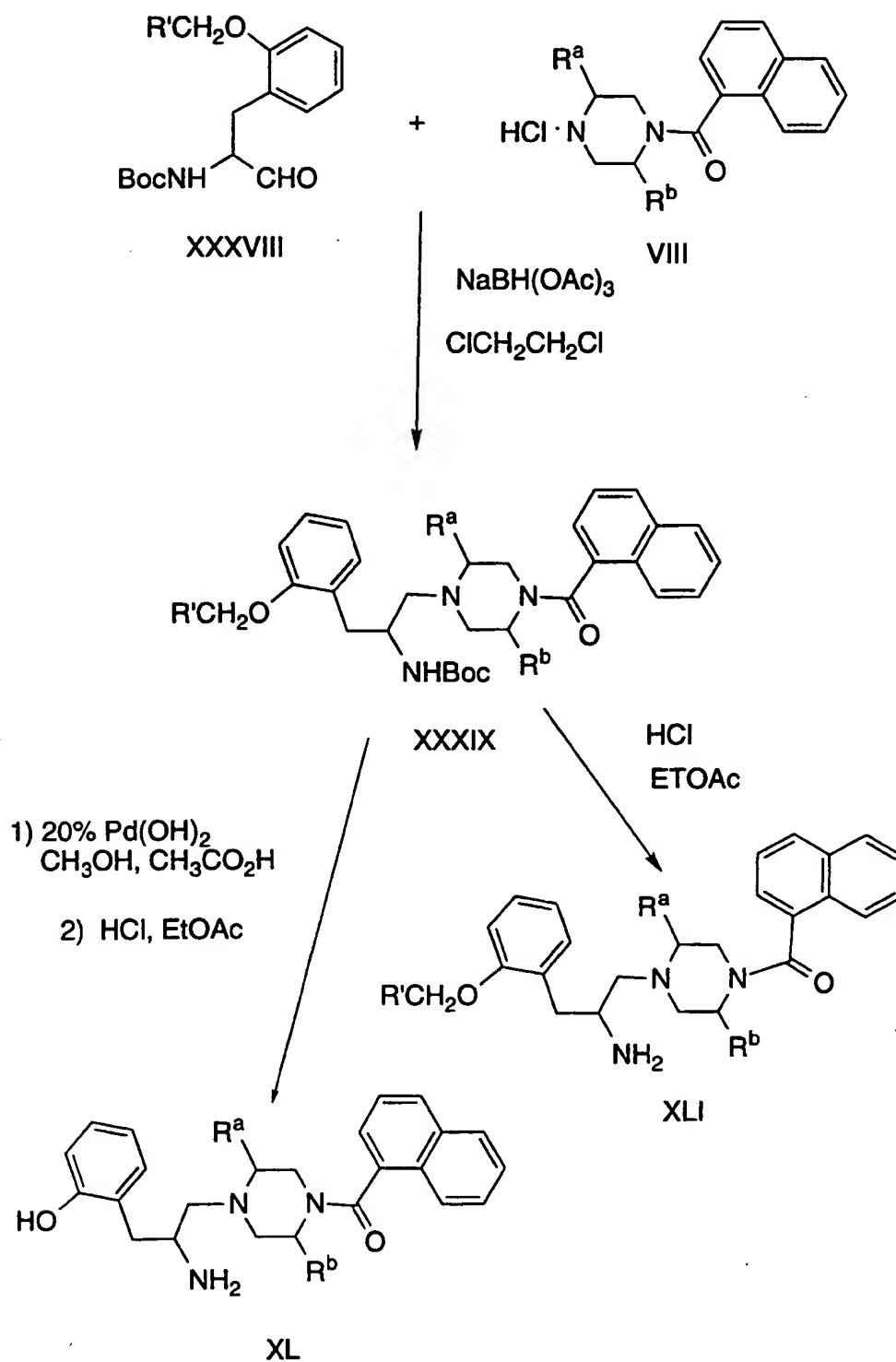
- 205 -

SCHEME 8

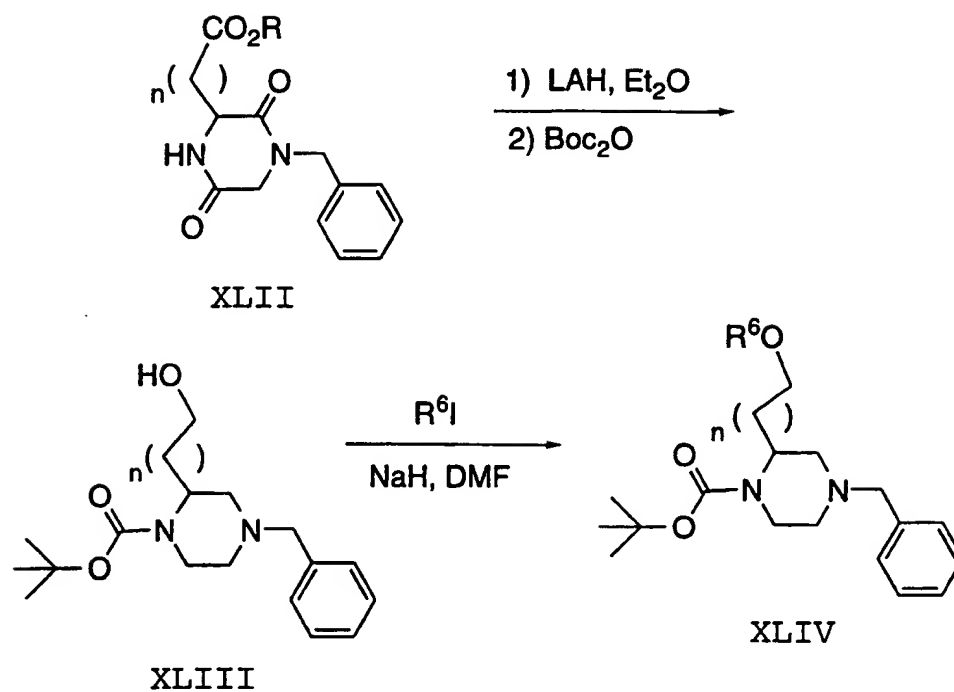
- 206 -

SCHEME 9

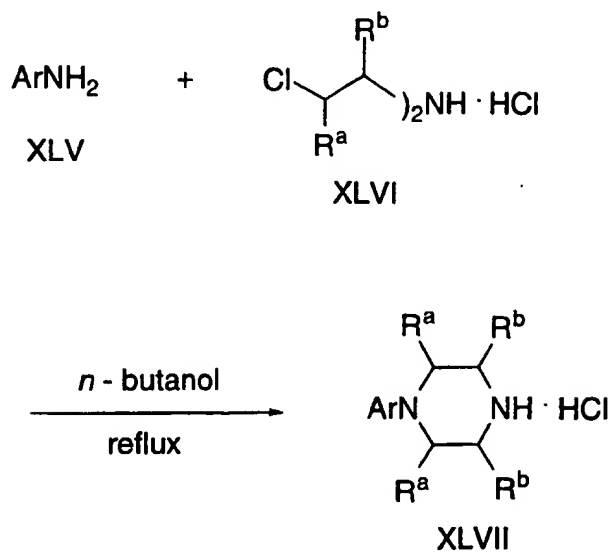
- 207 -

SCHEME 9 (continued)

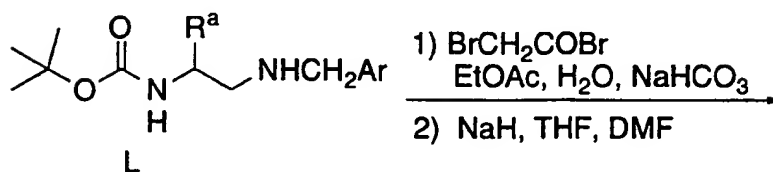
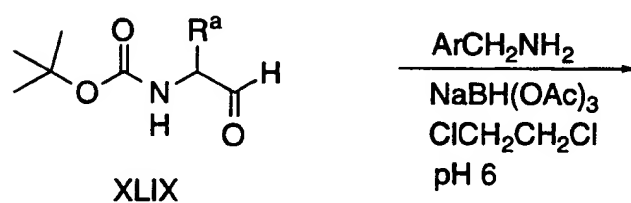
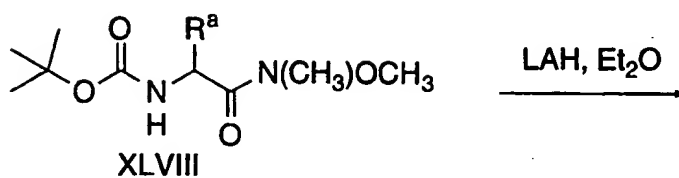
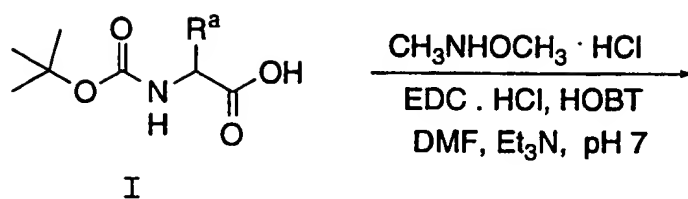
- 208 -

SCHEME 10

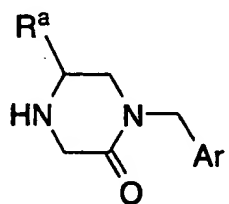
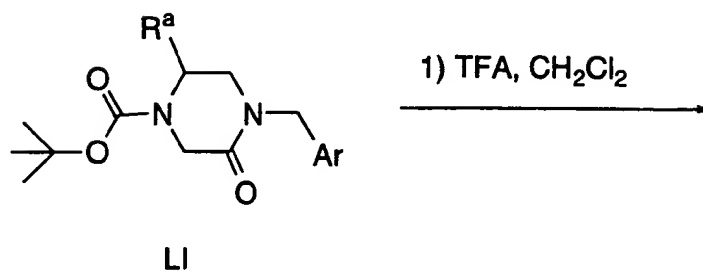
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SCHEME 11

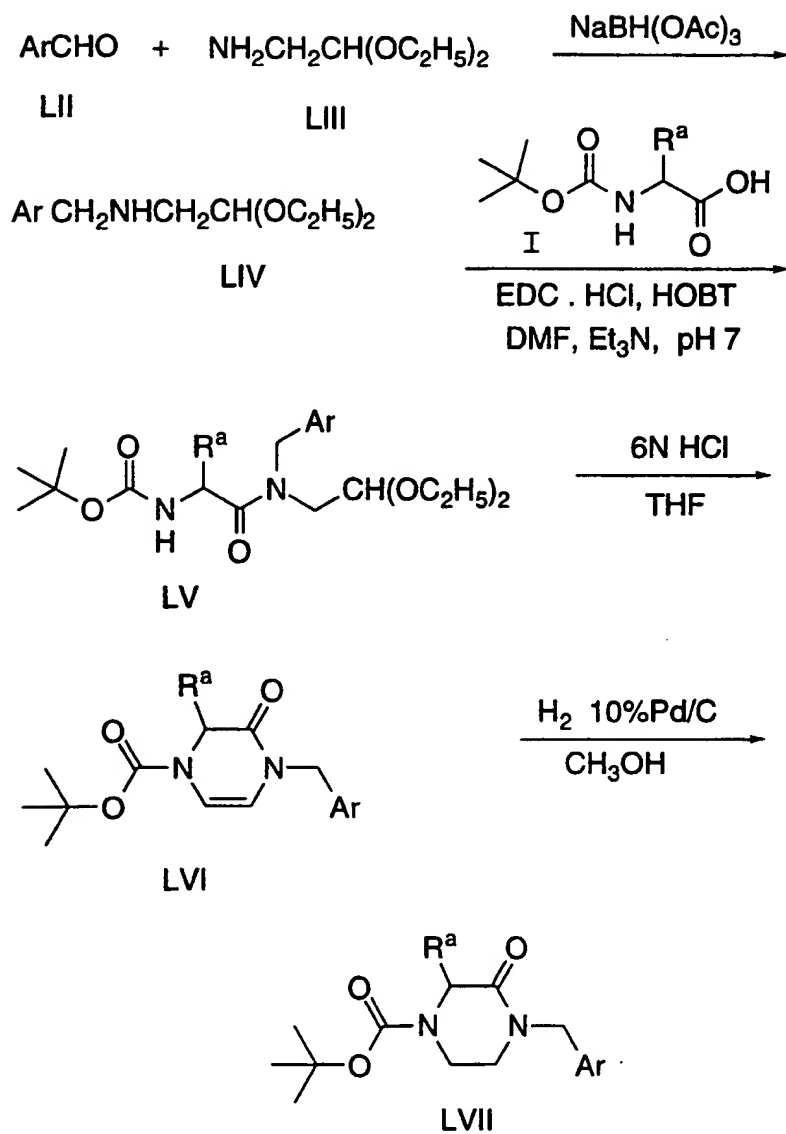
- 209 -

SCHEME 12

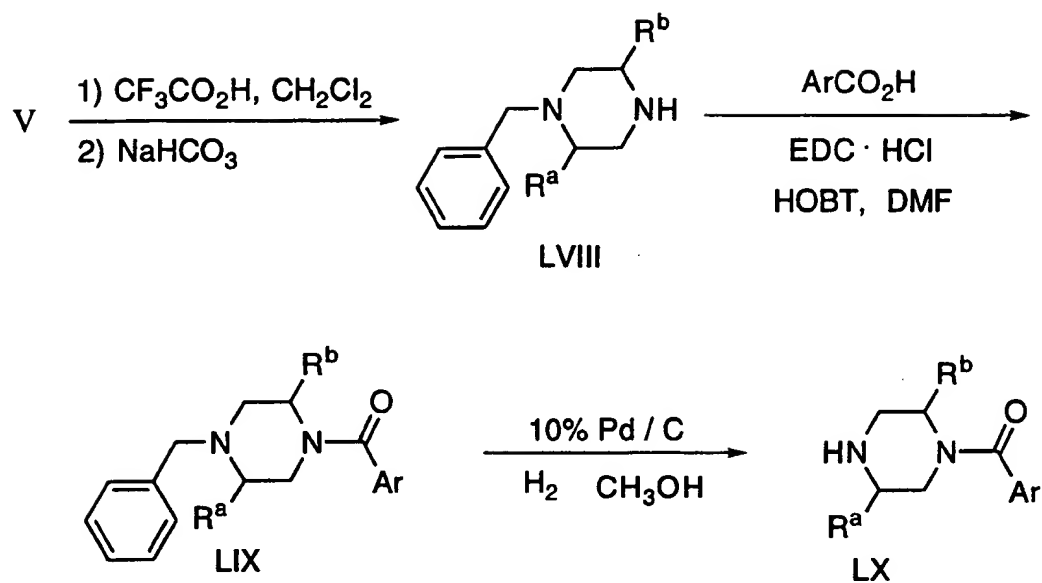
- 210 -

SCHEME 12 (CONT'D)

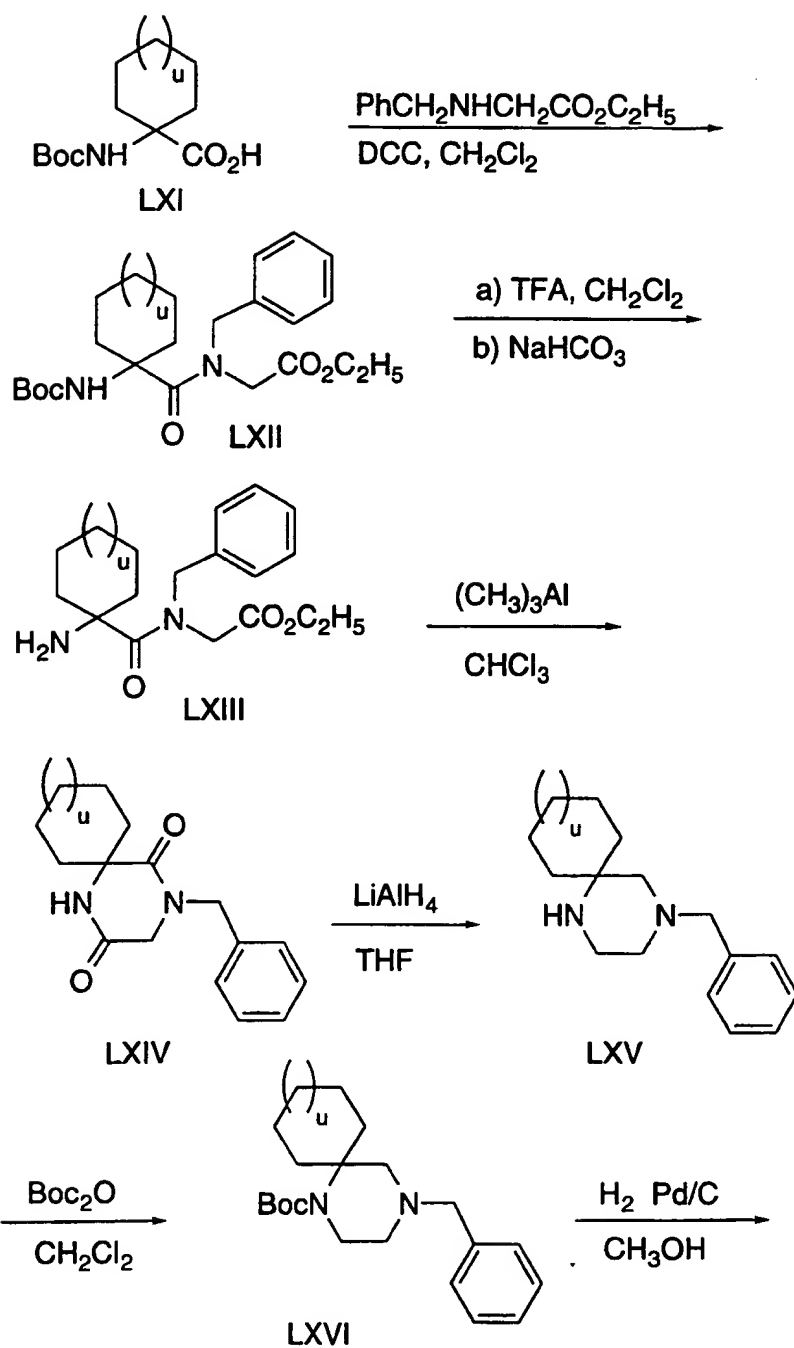
- 211 -

SCHEME 13

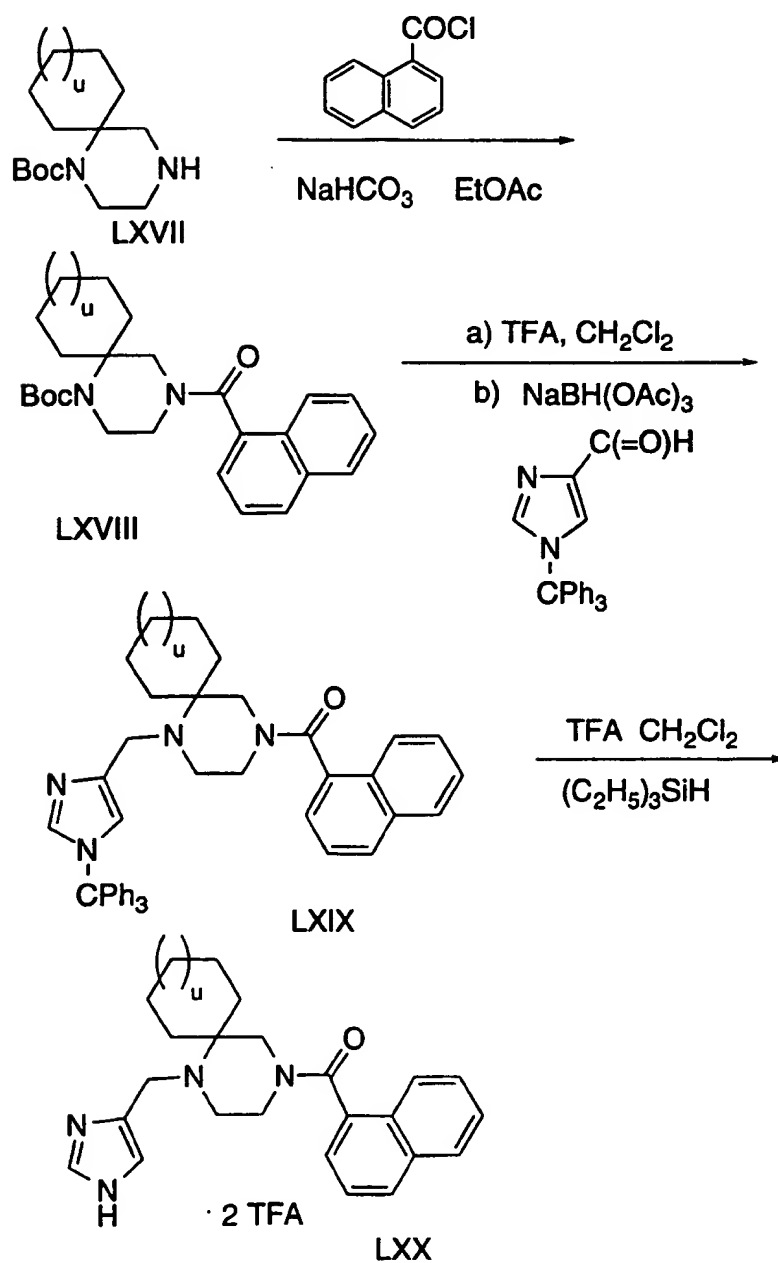
- 212 -

SCHEME 14

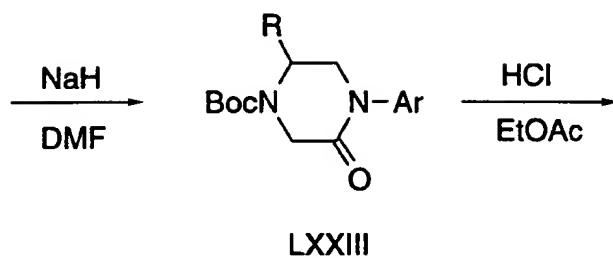
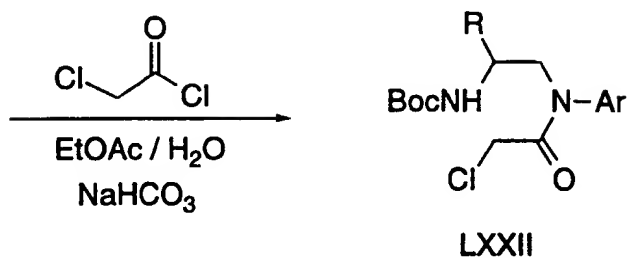
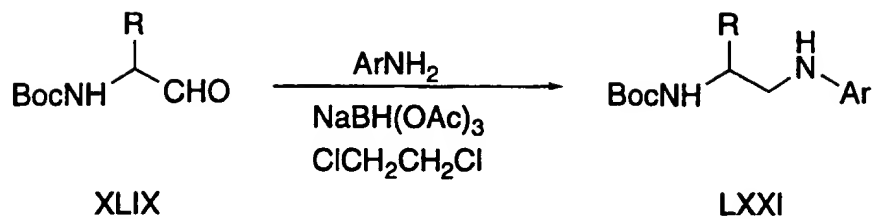
- 213 -

SCHEME 15

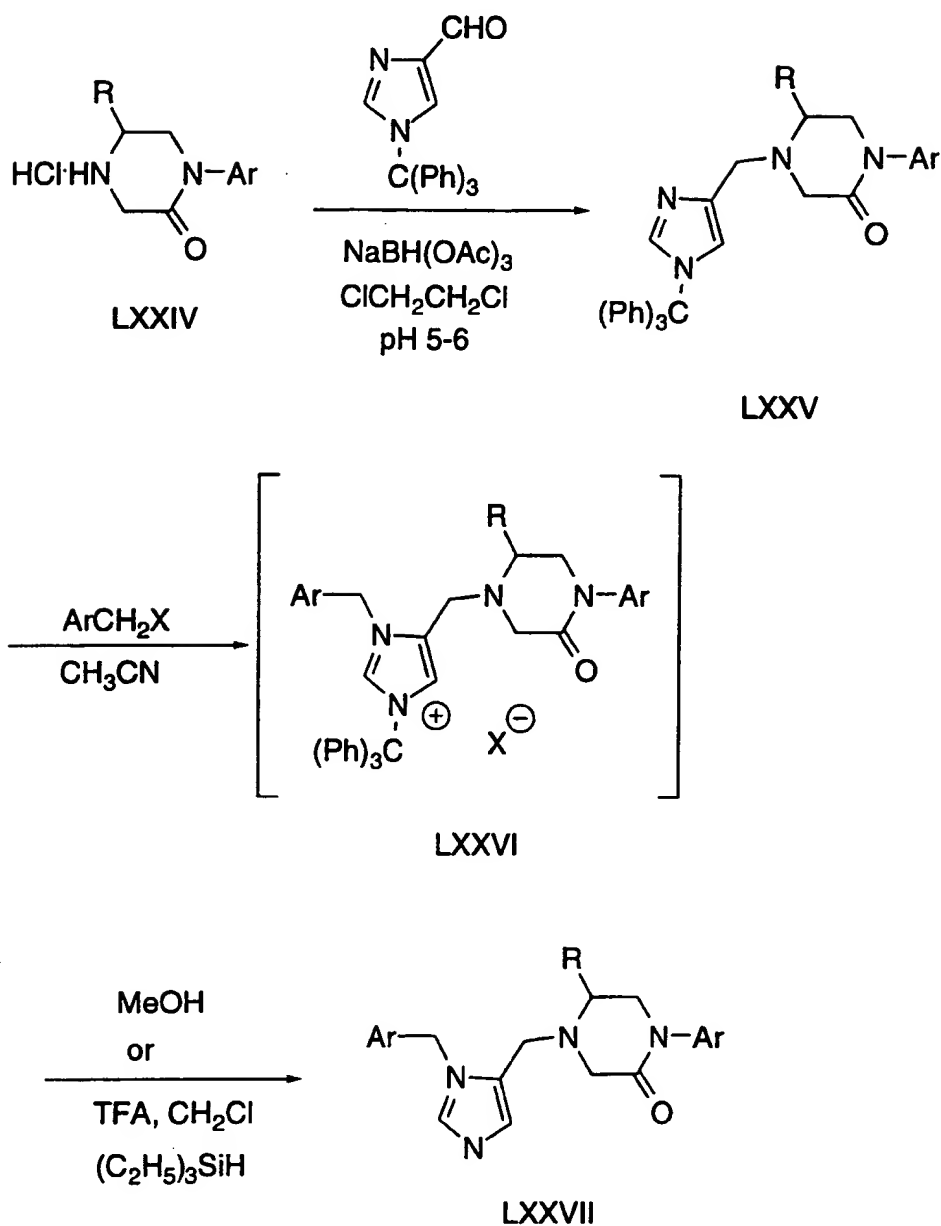
- 214 -

SCHEME 15 (continued)

- 215 -

SCHEME 16

- 216 -

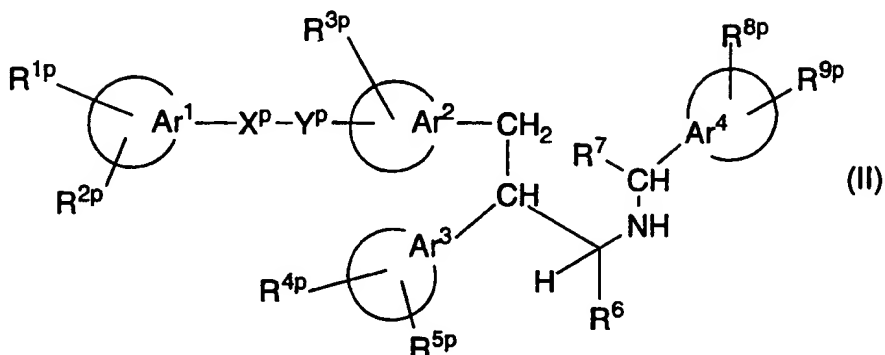
SCHEME 16 (continued)

The compound of the formula (gg) of the present invention
 5 can be prepared, for example, by the following process 1, 2, 3, 4, 5 or
 6.

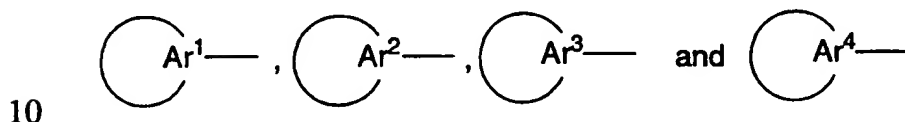
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Process 1

The compound of the formula (gg) can be prepared by
 5 reacting a compound of the formula (II):

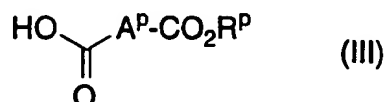


wherein each of

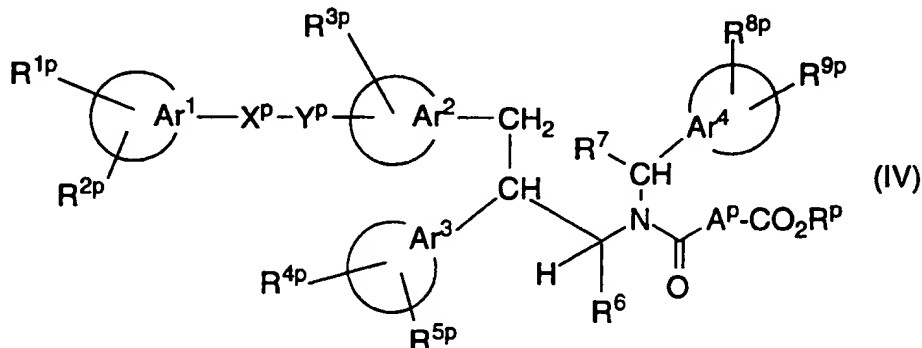


which are the same or different, is an aryl group or a heteroaromatic ring group; each of X^p and Y^p which are the same or different, is an oxygen atom, a sulfur atom, a carbonyl group or a group of the formula -CHR^a- (wherein R^a is a hydrogen atom or a lower alkyl group) or
 15 -NR^{bp}- (wherein R^{bp} is a hydrogen atom, a lower alkyl group or an imino-protecting group), or X^p and Y^p together represent a vinylene group or an ethynylene group; each of R^{1p}, R^{2p}, R^{3p}, R^{8p} and R^{9p} which are the same or different, is a hydrogen atom, a halogen atom, a hydroxyl group which may be protected, a lower alkyl group or a lower alkoxy group; each of R^{4p} and R^{5p} which are the same or different, is a
 20 hydrogen atom, a halogen atom, a nitro group, a cyano group, a lower alkoxy carbonyl group, a carbamoyl group, a lower alkyl carbamoyl group, a lower alkyl group, a lower fluoroalkyl group, a lower alkoxy group or a hydroxyl, amino, carboxyl or lower hydroxyalkyl group
 25 which may be protected; R⁶ is a lower alkyl group; and R⁷ is a

hydrogen atom or a lower alkyl group, provided that when one of XP and YP is an oxygen atom, a sulfur atom or a group of the formula -NR^{bp}- (wherein R^{bp} is as defined above), the other is a carbonyl group or a group of the formula -CHR^a- (wherein R^a is as defined above), with a carboxylic acid of the formula (III) or its reactive derivative:



wherein AP is a C₂-8 saturated or unsaturated aliphatic hydrocarbon group which may have substituent(s) selected from the group consisting of a lower alkyl group, a lower alkoxy group, an aryl group, an aralkyl group, and hydroxyl, lower hydroxyalkyl, carboxyl and lower carboxyalkyl groups which may be protected; and RP is a hydrogen atom or a carboxyl-protecting group, to obtain a compound of the formula (IV):



wherein $\bigcirc\text{Ar}^1\text{—}$, $\bigcirc\text{Ar}^2\text{—}$, $\bigcirc\text{Ar}^3\text{—}$, \dots , $\bigcirc\text{Ar}^4\text{—}$

AP, XP, YP, R¹p, R²p, R³p, R⁴p, R⁵p, R⁶, R⁷, R⁸p, R⁹p and RP are as defined above, and, if necessary, removing any protecting group.

As the reactive derivative of the carboxylic acid of the formula (III), an acid halide, a mixed acid anhydride, an active ester or an active amide may, for example, be used. When the carboxylic acid of the formula (III) is used, it is preferred to conduct the reaction in the presence of a condensing agent such as *N,N'*-

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dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide or 2-chloro-1,3-dimethylimidazolyl chloride.

The reaction of the compound of the formula (II) with the carboxylic acid of the formula (III) or its reactive derivative, is conducted usually by using 1 mol or an excess molar amount, preferably from 1 to 5 mols, of the carboxylic acid of the formula (III) or its reactive derivative, per mol of the compound of the formula (II).

The reaction is conducted usually in an inert solvent. The inert solvent may, for example, be a halogenated hydrocarbon such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane or trichloroethylene; an ether such as ethyl ether, tetrahydrofuran or dioxane; an aromatic hydrocarbon such as benzene, toluene, chlorobenzene or xylene; an aprotic polar solvent such as dimethylformamide, acetonitrile, acetone, ethyl acetate or hexamethylphosphoric triamide, or a mixture of such solvents.

The reaction temperature is usually from -70°C to the boiling point of the solvent used for the reaction, preferably from -20°C to 100°C.

The reaction time is usually from 5 minutes to 7 days, preferably from 10 minutes to 24 hours.

The above reaction can be conducted in the presence of a base to facilitate the reaction.

As such a base, it is preferred to conduct the reaction in the presence of an inorganic base such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate or sodium hydrogen carbonate, or an organic base such as triethylamine, N-ethyl-diisopropylamine, pyridine, 4-dimethylaminopyridine or N,N-dimethylaniline.

Such a base is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the reactive derivative of the carboxylic acid of the formula (III).

The acid halide of the compound of the formula (III) can be obtained by reacting the carboxylic acid of the formula (III) with a

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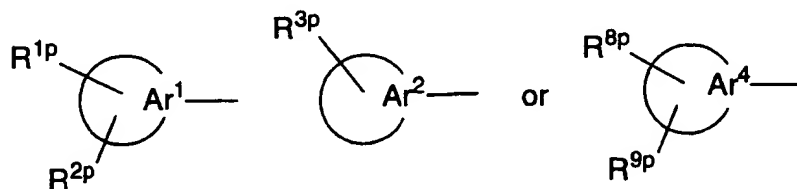
halogenating agent in accordance with a conventional method. As the halogenating agent, thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, phosphorus tribromide, oxalyl chloride or phosgene may, for example, be used.

5 The mixed acid anhydride of the compound of the formula (III) can be obtained by reacting the carboxylic acid of the formula (III) with an alkyl chlorocarbonate such as ethyl chlorocarbonate or with an aliphatic carboxylic acid chloride such as acetyl chloride, in accordance with a conventional method. Further, an intramolecular acid anhydride
10 may be formed between carboxyl groups at both terminals, or when in the formula (III), a carboxyl group is present on the saturated or unsaturated aliphatic hydrocarbon group for AP, an intramolecular acid anhydride may be formed between such a carboxyl group and a carboxyl group to be involved in the reaction, to constitute a reactive
15 derivative of the carboxylic acid.

The active ester of the compound of the formula (III) can be prepared by reacting the carboxylic acid of the formula (III) with an N-hydroxy compound such as N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxybenzotriazole, or a phenol compound
20 such as a 4-nitrophenol, 2,4-dinitrophenol, 2,4,5-trichlorophenol or pentachlorophenol, in the presence of a condensing agent such as N,N'-dicyclohexylcarbodiimide or 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide in accordance with a conventional method.

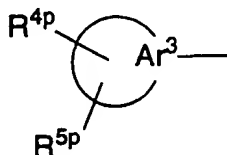
25 The active amide of the compound of the formula (III) can be prepared by reacting the carboxylic acid of the formula (III) with e.g. 1,1'-carbonyldiimidazole or 1,1'-carbonylbis(2-methylimidazole) in accordance with a conventional method.

30 When a hydroxyl group is present on the group of the formula



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when a hydroxyl group, a lower hydroxyalkyl group, a carboxyl group or a lower carboxyalkyl group is present on the saturated or unsaturated aliphatic hydrocarbon group represented by AP, and when a hydroxyl group, an amino group, a carboxyl group or a lower hydroxyalkyl group is present on the group of the formula



it is preferred to conduct the reaction after protecting such a hydroxyl group, a lower hydroxyalkyl group, an amino group, a carboxyl group or a lower carboxyalkyl group appropriately by a hydroxyl-protecting group, an amino-protecting group or a carboxyl-protecting group and removing the protecting group after the reaction. Further, in a case where one of XP and YP is a group of the formula -NR^{bp}- (wherein R^{bp} is as defined above), and the other is a group of the formula -CHR^a- (wherein R^a is as defined above), R^{bp} is preferably a lower alkyl group or an imino-protecting group, and when R^{bp} is an iminoprotecting group, it is preferred to remove such a protecting group after the reaction.

The hydroxyl-protecting group may, for example, be a lower alkylsilyl group such as a trimethylsilyl group or a tert-butyldimethylsilyl group; a lower alkoxymethyl group such as a methoxymethyl group or a 2-methoxyethoxymethyl group; a tetrahydropyranyl group; an aralkyl group such as a benzyl group, a p-methoxybenzyl group, a p-nitrobenzyl group or a trityl group; or an acyl group such as a formyl group or an acetyl group. Particularly preferred is a methoxymethyl group, a tetrahydropyranyl group, a trityl group, a tert-butyldimethylsilyl group or an acetyl group.

The amino- or imino-protecting group may, for example, be an aralkyl group such as a benzyl group, a p-methoxybenzyl group, a p-nitrobenzyl group, a benzhydryl group or a trityl group; a lower alkanoyl group such as a formyl group, an acetyl group, a propionyl

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group, a butyryl group or a pivaloyl group; a lower haloalkanoyl group such as a trifluoroacetyl group; a lower alkoxy carbonyl group such as a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group or a tert-butoxycarbonyl group; a lower haloalkoxy carbonyl group such as a 2,2,2-trichloroethoxycarbonyl group; an alkenyloxy carbonyl group such as a 2-propenyloxy carbonyl group; an aralkyloxy carbonyl group such as a benzyloxy carbonyl group or a p-nitrobenzyloxy carbonyl group; or a lower alkylsilyl group such as a trimethylsilyl group or a tert-butyldimethylsilyl group. Further the amino-protecting group may, for example, be an aralkylidene group such as a benzylidene group, a p-chlorobenzylidene group or a p-nitrobenzylidene group. Particularly preferred is an acetyl group, a trifluoroacetyl group, a tert-butoxycarbonyl group or a benzyloxy carbonyl group.

The carboxyl-protecting group may, for example, be a lower alkyl group such as a methyl group, an ethyl group, a propyl group, an isopropyl group or a tert-butyl group; a lower haloalkyl group such as a 2,2,2-trichloroethyl group; a lower alkenyl group such as 2-propenyl group; or an aralkyl group such as a benzyl group, a p-methoxybenzyl group, a p-nitrobenzyl group, a benzhydryl group or trityl group. Particularly preferred is a methyl group, an ethyl group, a tert-butyl group, a 2-propenyl group, a benzyl group, a p-methoxybenzyl group or a benzhydryl group.

After completion of the reaction, conventional treatment is conducted to obtain a crude product of the compound of the formula (IV). The compound of the formula (IV) may or may not be purified in accordance with a conventional method, and if necessary, reactions for removing protecting groups such as a hydroxyl group, an amino group and a carboxyl group, are appropriately conducted to obtain a compound of the formula (gg).

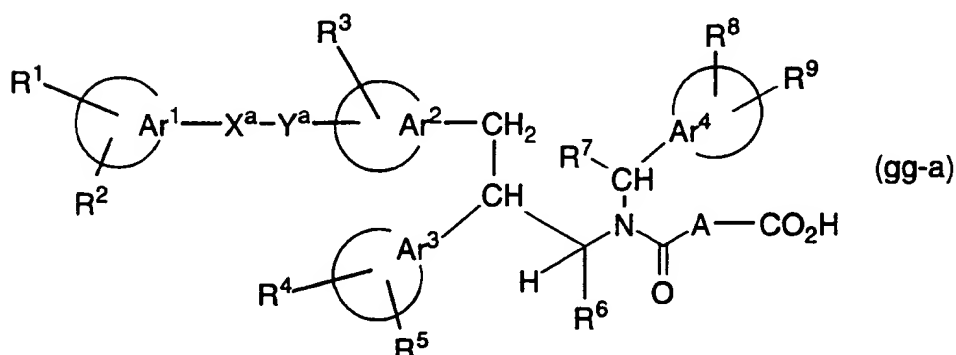
Removal of protecting groups may vary depending upon their types, but can be conducted in accordance with the methods disclosed in a literature (Protective Groups in Organic Synthesis, T.W. Greene, John Wiley & Sons (1981)) or methods similar thereto, for

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example by solvolysis employing an acid or a base, by chemical reduction employing a metal hydride complex or by catalytic reduction employing a palladium-carbon catalyst or Raney nickel.

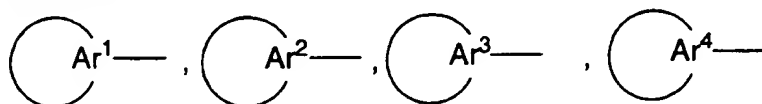
5 Process 2

A compound of the formula (gg-a):



10

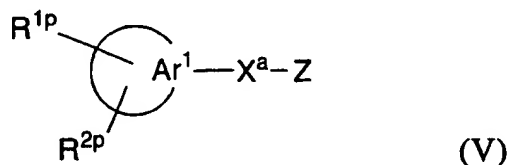
wherein



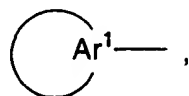
A, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are as defined above, and X^a and Y^a are as defined below, can be prepared by reacting a

15

compound of the formula (V):



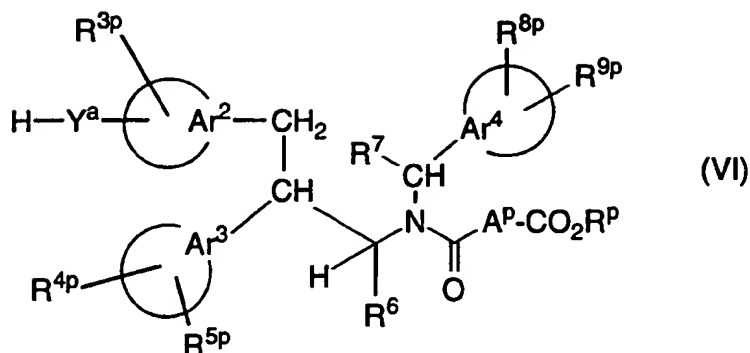
wherein X^a is a carbonyl group or a group of the formula -CHR^a- (wherein R^a is as defined above), Z is a leaving group; and



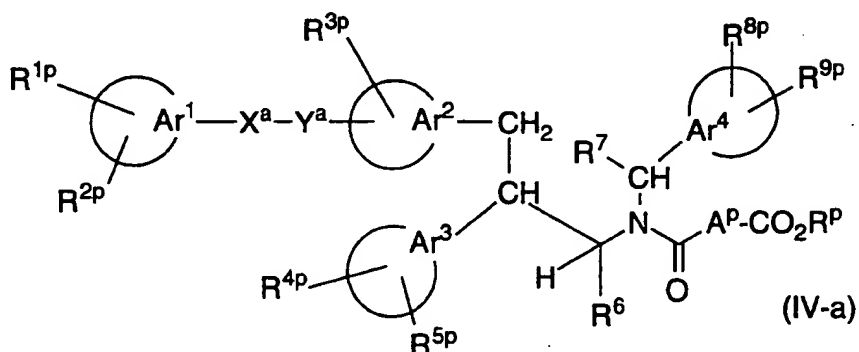
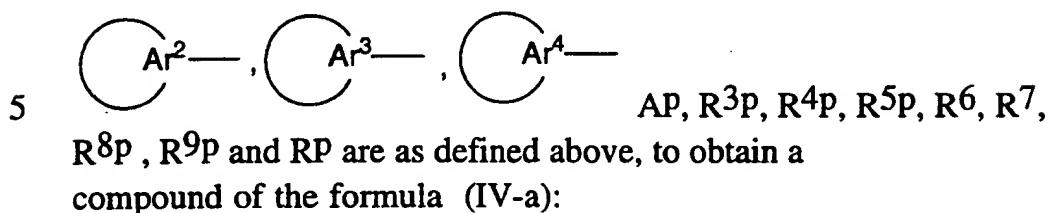
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R^{1p} and R^{2p} are as defined above, with a compound of the formula (VI):

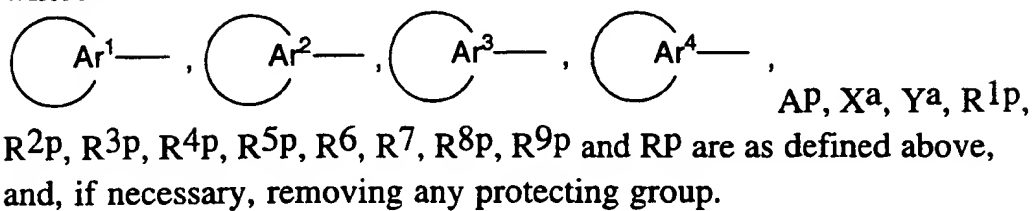
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wherein Y^a is an oxygen atom, a sulfur atom or a group of the formula $-NR^b-$ (wherein R^b is as defined above); and



10 wherein



15 Process 2 is a process for preparing a compound of the
 formula (gg) wherein $-X-Y-$ is a group of the formula $-COO-$, $-COS-$,

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-CONR^b-, -CHR^aO-, -CHR^aS- or -CHR^aNR^b- (wherein R^a and R^b are as defined above) i.e. a compound of the formula (gg-a).

The reaction of the compound of the formula (V) with a compound of the formula (VI) is carried out usually by using 1 mol or an excess molar amount, preferably from 1 to 3 mols, of the compound of the formula (V), per mol of the compound of the formula (VI).

The reaction is conducted usually in an inert solvent. The inert solvent may, for example, be a halogenated hydrocarbon such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane or trichloroethylene; an ether such as ethyl ether, tetrahydrofuran or dioxane; an aromatic hydrocarbon such as benzene, toluene, chlorobenzene or xylene; an aprotic polar solvent such as dimethylformamide, acetonitrile, acetone, ethyl acetate or hexamethylphosphoric triamide, or a mixture of such solvents.

The reaction temperature is usually from -70°C to the boiling point of the solvent used for the reaction, preferably from -20°C to 100°C.

The reaction time is usually from 5 minutes to 7 days, preferably from 10 minutes to 24 hours.

The above reaction is preferably conducted in the presence of a base to facilitate the reaction. Especially when Y^a in the formula (VI) is not a group of the formula -NR^b-, it is necessary to carry out the reaction in the presence of an inorganic base such as sodium hydride, n-butyl lithium, sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate or sodium hydrogen carbonate, or an organic base such as triethylamine, N-ethyl-diisopropylamine, pyridine, 4-dimethylaminopyridine or N,N-dimethylaniline.

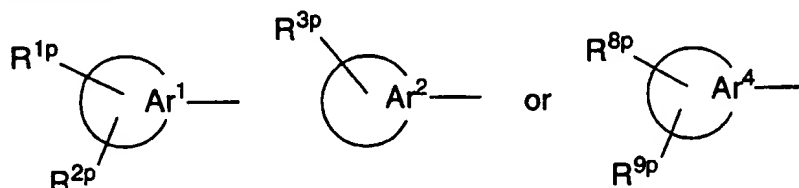
The base is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the compound of the formula (V).

The leaving group represented by Z in the formula (V)

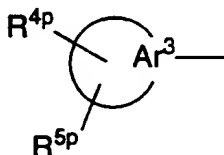
- 226 -

may, for example, be a halogen atom such as a chlorine atom, a bromine atom or an iodine atom, or an organic sulfonyloxy group such as a methanesulfonyloxy group, a p-toluenesulfonyloxy group or a benzenesulfonyloxy group.

- 5 When a hydroxyl group is present on the group of the formula



- when a hydroxyl group, a lower hydroxyalkyl group, a carboxyl group or a lower carboxyalkyl group is present on the saturated or unsaturated aliphatic hydrocarbon group represented by AP, and when a hydroxyl group, an amino group, a carboxyl group or a lower hydroxyalkyl group is present on the group of the formula
- 10



- 15 it is preferred to conduct the reaction after protecting such a hydroxyl group, a lower hydroxyalkyl group, an amino group, a carboxyl group or a lower carboxyalkyl group appropriately by a hydroxyl-protecting group, an amino-protecting group or a carboxyl-protecting group and removing any protecting group after the reaction.
- 20

The hydroxyl-protecting group, the amino-protecting group and the carboxyl-protecting group may be the protecting groups mentioned above with respect to process 1.

- After completion of the reaction, a usual treatment is carried out to obtain a crude product of the compound of the formula (IV-a). The compound of the formula (IV-a) thus obtained may or may not be purified by a conventional method, and if necessary, reactions for removing the hydroxyl-, amino- and carboxyl-protecting groups may be
- 25

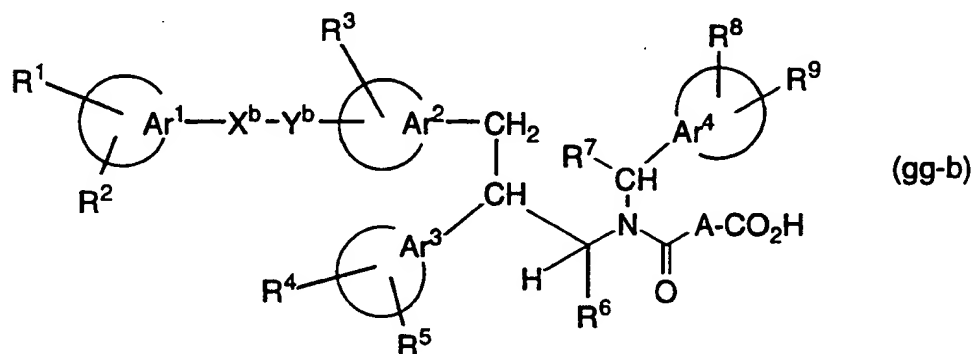
- 227 -

carried out in a proper combination to obtain a compound of the formula (gg-a).

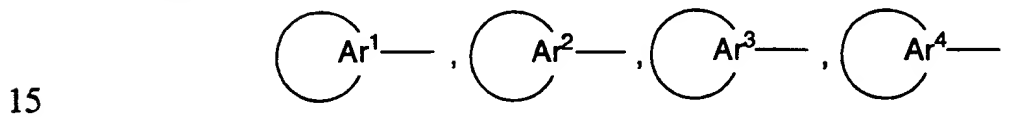
- 5 The method for removing a protecting group varies depending upon the type of the protecting group and the stability of the desired compound (gg-a). However, removal of protecting groups can be appropriately conducted in accordance with the methods disclosed in the above-mentioned literature or methods similar thereto.

10 Process 3

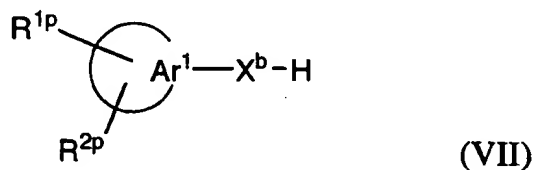
A compound of the formula (gg-b):



wherein

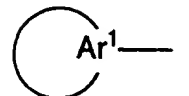


A, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are as defined above, and X^b and Y^b are as defined below, can be prepared by reacting a compound of the formula (VII):

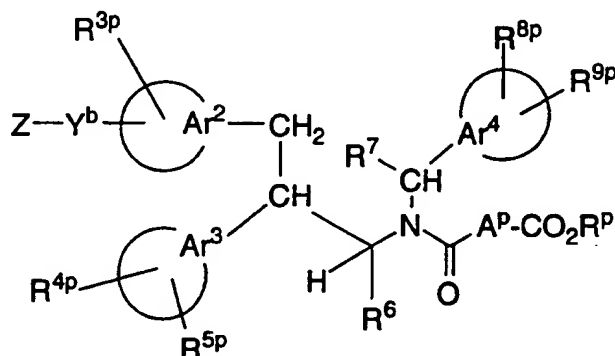


- 228 -

wherein X^b is an oxygen atom, a sulfur atom or a group of the formula

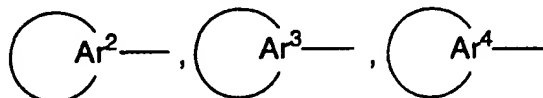


$-\text{NR}^b-$ (wherein R^b is as defined above); and R^{1p} and R^{2p} are as defined above, with a compound of the formula (VIII):

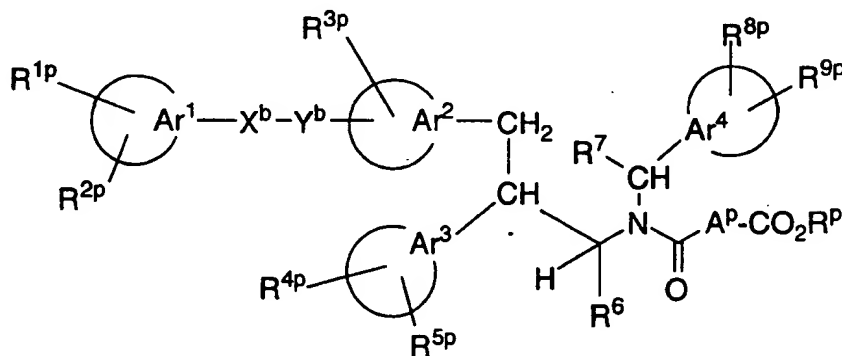


5 (VIII)

wherein Y^b is a carbonyl group or a group of the formula $-\text{CHRA}^a-$ (wherein R^a is as defined above); and



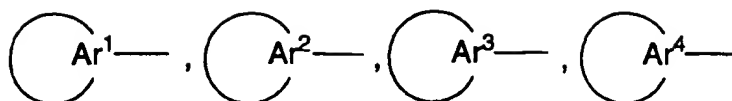
10 , AP , Z , R^{3p} , R^{4p} , R^{5p} , R^6 , R^7 , R^{8p} , R^{9p} and R^p are as defined above, to obtain a compound of the formula (IV-b):



(IV-b)

15

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wherein

AP, X^b, Y^b, R¹P, R²P, R³P, R⁴P, R⁵P, R⁶, R⁷, R⁸P, R⁹P and RP are as

defined above, and, if necessary, removing any protecting

5 group.

Process 3 is a process for preparing a compound of the formula (gg) wherein -X-Y- is a group of the formula -OCO-, -SCO-, -NR^bCO-, -OCHRA^a-, -SCHRA^a- or -NR^bCHRA^a- (wherein R^a and R^b are as defined above) i.e. a compound of the formula (I-b).

10 This process can be conducted usually in an inert solvent, preferably in the presence of a base, by using 1 mol or an excess molar amount, preferably from 1 to 3 mols, of the compound of the formula (VII), per mol of the compound of the formula (VIII). The types of the inert solvent and the base as well as the reaction conditions may be the
15 same as described above with respect to process 2. Accordingly, the reaction and the post-treatment after the reaction may preferably be carried out all in accordance with process 2.

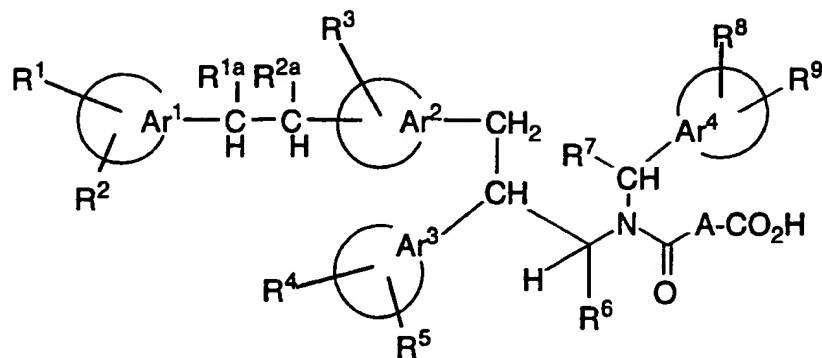
Further, in the above processes 2 and 3, when X^a or Y^b is a carbonyl group, a compound wherein the group corresponding to Z is a hydroxyl group i.e. a compound wherein Z and the adjacent X^a or Y^b together represents a carboxyl group, can be used. In such a case the reaction conditions, etc. are preferably in accordance with the reaction conditions for the reaction of the compound of the formula (II) with the compound of the formula (III) in the above process 1.

25

Process 4

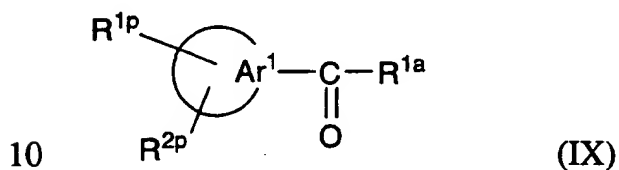
A compound of the formula (gg-c):

- 230 -



gg-c

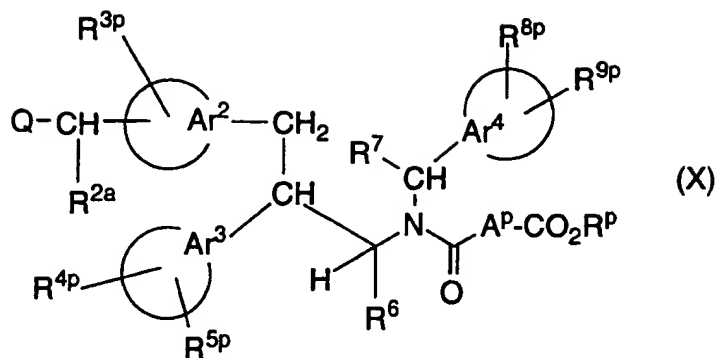
- 5 wherein Ar^1 —, Ar^2 —, Ar^3 —, Ar^4 —, A, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are as defined above, and R^{1a} and R^{2a} are as defined below, can be prepared by reacting a compound of the formula (IX):



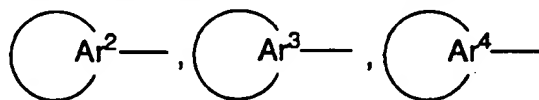
wherein R^{1a} is a hydrogen atom or a lower alkyl group; and

Ar^1 —, R^{1p} and R^{2p} are as defined above, with a compound of the formula (X):

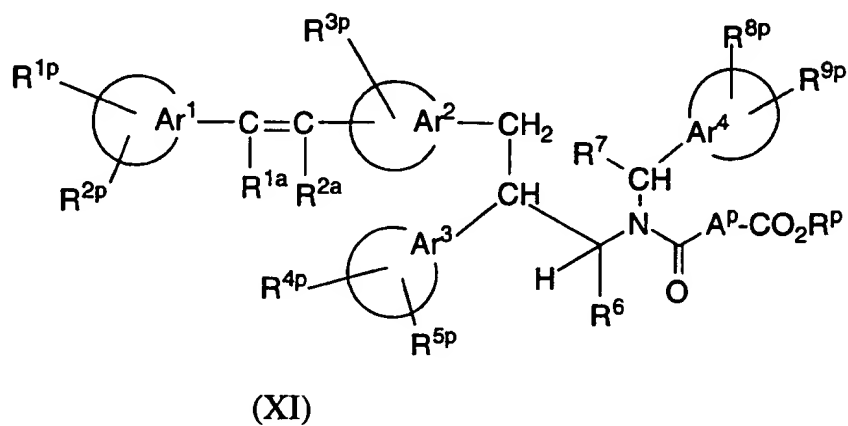
- 231 -



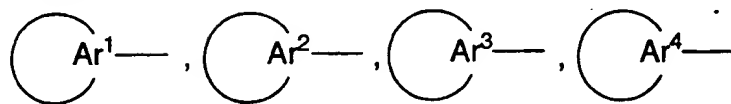
wherein Q is a triphenylphosphonio group, a dimethoxyphosphoryl group or a diethoxyphosphoryl group; R^{2a} is a hydrogen atom or a



lower alkyl group; and AP,
R^{3p}, R^{4p}, R^{5p}, R⁶, R⁷, R^{8p}, R^{9p} and R^P are as defined above, to
obtain a compound
of the formula (XI):



wherein



AP, R^{1p}, R^{2p}, R^{3p}, R^{4p}, R^{5p}, R⁶, R⁷, R^{8p}, R^{9p}, R^P, R^{1a} and R^{2a} are
as defined above, and, if necessary, removing any protecting group.

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Process 4 is a process for preparing a compound of the formula (gg) wherein -X-Y- is -CHR^{1a}CHR^{2a}- (wherein each of R^{1a} and R^{2a} which are the same or different, is a hydrogen atom or a lower alkyl group) i.e. a compound of the formula (gg-c).

5 The reaction of the compound of the formula (IX) with a compound of the formula (X) is carried out usually by employing equimolar amounts of the two reactants or using a slightly excess amount of one of them.

10 The reaction is carried out usually in an inert solvent. Such an inert solvent may, for example, be an ether such as ethyl ether, tetrahydrofuran or dioxane; an aromatic hydrocarbon such as benzene, toluene, chlorobenzene or xylene; an aprotic polar solvent such as dimethylformamide, acetonitrile, acetone, ethyl acetate or hexamethylphosphoric triamide; or a mixture of such solvents.

15 The reaction temperature is usually from -100°C to the boiling point of the solvent used for the reaction, preferably from -70°C to 50°C.

 The reaction time is usually from 5 minutes to 7 days, preferably from 10 minutes to 24 hours.

20 Further, the above reaction can be conducted in the presence of a base to facilitate the reaction. Especially when Q in the formula (X) is a triphenylphosphonio group, the reaction is preferably conducted in the presence of a base such as sodium hydride, n-butyl lithium, sodium methoxide, potassium tert-butoxide, sodium hydroxide or potassium hydroxide.

25 Such a base is used in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols per mol of the compound wherein Q is a triphenylphosphonio group.

30 The reaction of reducing the compound of the formula (XI) obtained in the above step is usually preferably conducted by catalytic reduction employing a palladium carbon catalyst, a Raney nickel catalyst or a platinum catalyst in an inert solvent.

 The inert solvent may, for example, be an alcohol such as methanol, ethanol or propanol, or acetic acid.

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The reaction temperature is usually from -20°C to 100°C, preferably from 0°C to room temperature.

The reaction time is usually from 5 minutes to 7 days, preferably from 10 minutes to 24 hours.

5 The hydrogen pressure in the catalytic reduction reaction is usually preferably from atmospheric pressure to 5 atm, and the amount of the catalyst is usually from 0.01 to 1 mol, preferably from 0.05 to 0.2 mol, per mol of the starting material compound (XI).

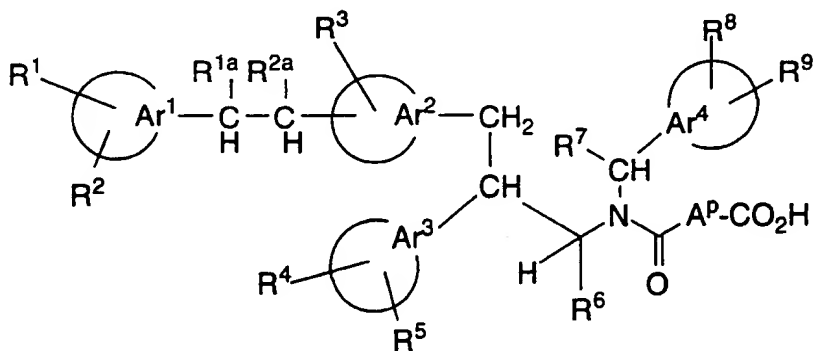
10 After completion of the reaction, the product is subjected to a usual treatment after removing any protecting group if such a protecting group is present or directly if no such protecting group is present, to obtain a compound of the formula (gg-c).

15 Removal of the protecting group and the post treatment may be conducted by the methods described with respect to the above process 1.

Process 5

A compound of the formula (gg-c):

20

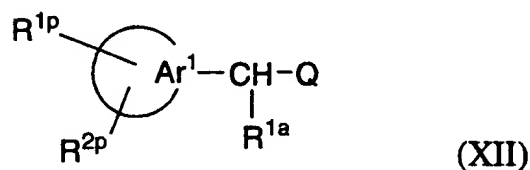


gg-c

wherein \bigcirc_{Ar^1} , \bigcirc_{Ar^2} , \bigcirc_{Ar^3} , \bigcirc_{Ar^4} ,

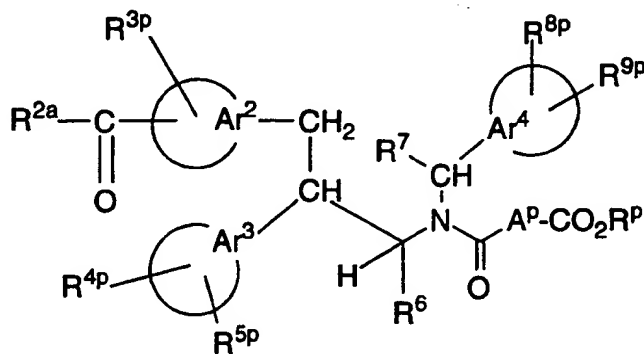
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A, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹, R^{1a} and R^{2a} are as defined above, can be obtained by reacting a compound of the formula (XII):



5

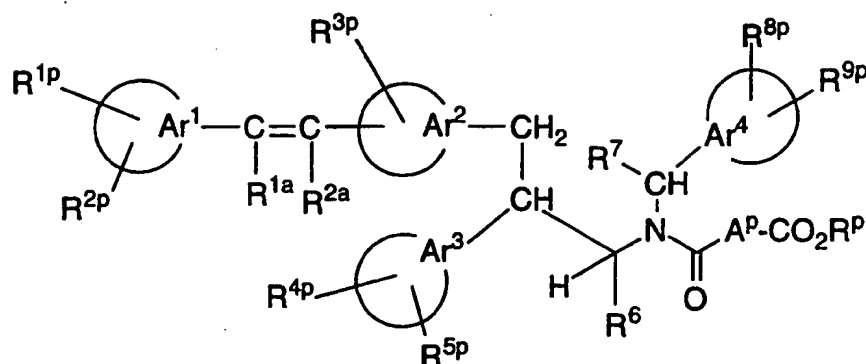
wherein $\text{---} \text{Ar}^1 \text{---}$, Q, R^{1p}, R^{2p} and R^{1a} are as defined above, with a compound of the formula (XIII):



10 (XIII)

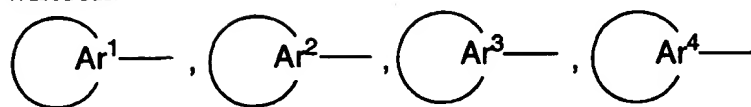
wherein $\text{---} \text{Ar}^2 \text{---}$, $\text{---} \text{Ar}^3 \text{---}$, $\text{---} \text{Ar}^4 \text{---}$, AP, R^{3p}, R^{4p}, R^{5p}, R⁶, R⁷, R^{8p}, R^{9p}, R^p and R^{2a} are as defined above, to obtain a compound of the formula (XI):

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(XI)

wherein

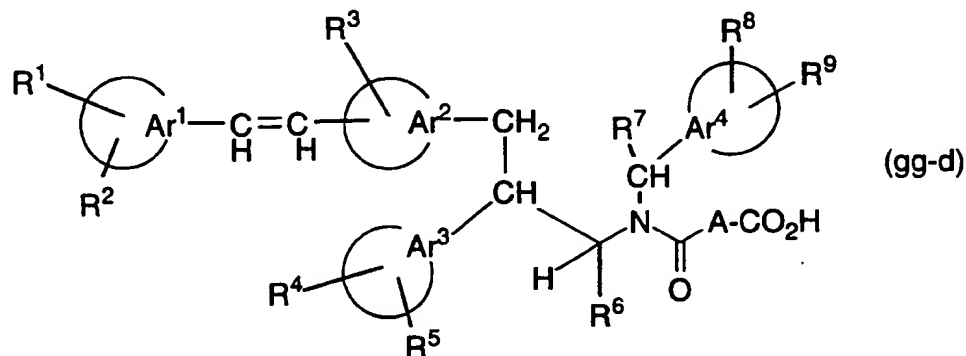


- 5 AP, R^{1p}, R^{2p}, R^{3p}, R^{4p}, R^{5p}, R⁶, R⁷, R^{8p}, R^{9p}, R^p, R^{1a} and R^{2a} are as defined above, then reducing the compound of the formula (XI), and, if necessary, removing any protecting group.

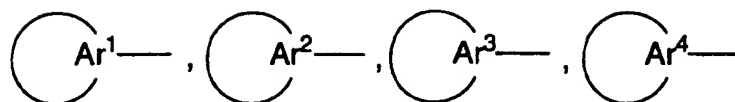
- 10 Like process 4, process 5 is a process for producing a compound of the formula (gg) wherein -X-Y- is -CHR^{1a}CHR^{2a}. (wherein R^{1a} and R^{2a} are as defined above) i.e. a compound of the formula (gg-c).

- 15 Process 5 is equal to the reaction of process 4 wherein starting material compounds (IX) and (X) are replaced by the compounds (XIII) and (XII), respectively. Accordingly, the manner and conditions of the reaction may be all in accordance with process 4.

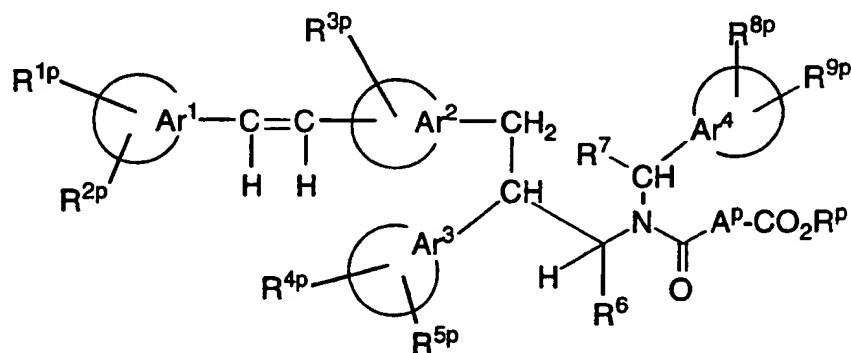
Further, a compound of the formula (gg-d):



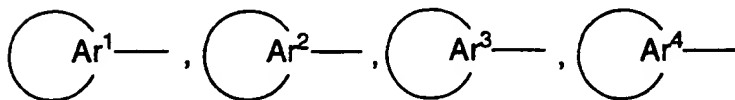
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wherein Ar^1 , Ar^2 , Ar^3 , Ar^4 , A, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 are as defined above, can be obtained by removing a protecting group, as the case requires, from a compound of the formula (XI-a):



(XI-a)



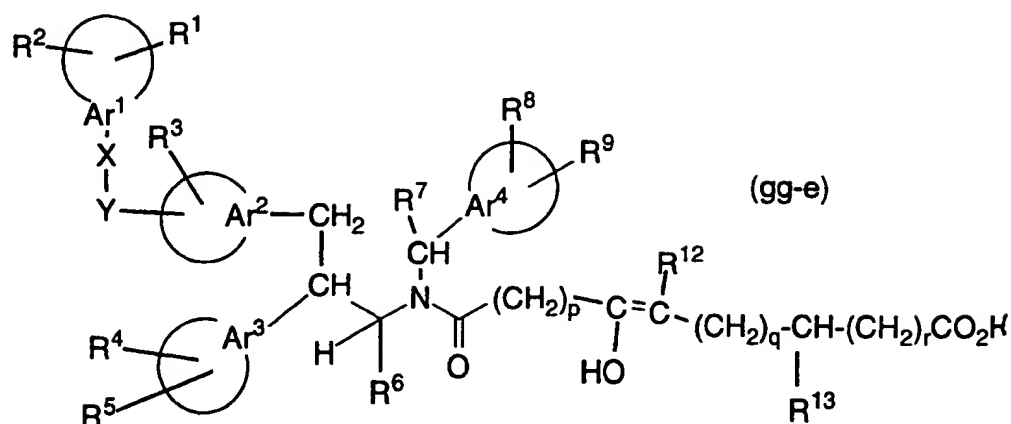
wherein Ar^1 , Ar^2 , Ar^3 , Ar^4 , AP, R^{1p} , R^{2p} , R^{3p} , R^{4p} , R^{5p} , R^6 , R^7 , R^{8p} , R^{9p} and R^p are as defined above, i.e. a compound of the formula (XI) wherein both R^{1a} and R^{2a} are hydrogen atoms, among compounds of the formula (XI) obtainable as intermediates in the above processes 4 and 5.

Process 6

15

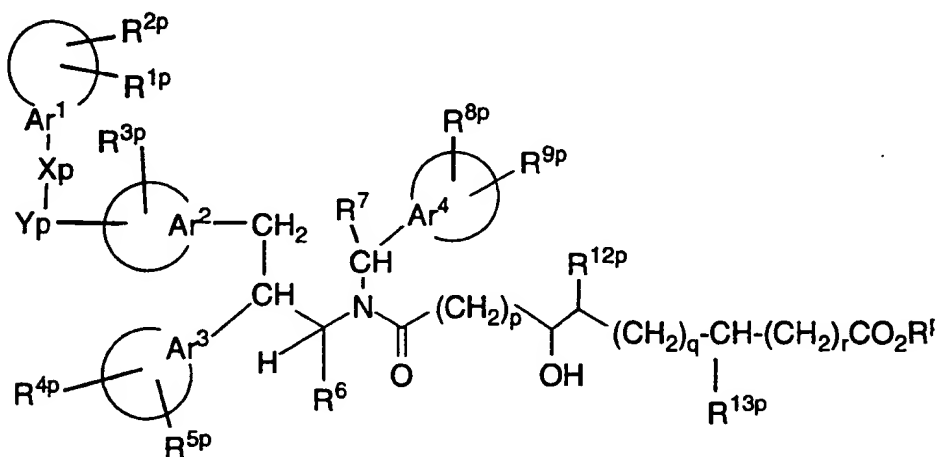
A compound of the formula (gg-e):

- 237 -



wherein $\bigcirc\text{Ar}^1\text{---}$, $\bigcirc\text{Ar}^2\text{---}$, $\bigcirc\text{Ar}^3\text{---}$, $\bigcirc\text{Ar}^4\text{---}$, X, Y,

5 R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹², R¹³, p, q and r are as defined above, can be prepared by oxidizing a compound of the formula (IV-e):



(IV-e)

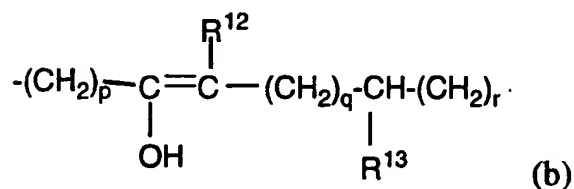
10 wherein R^{12p} is a hydrogen atom or a lower hydroxyalkyl or carboxyl group which may be protected, R^{13p} is a hydrogen atom or a hydroxyl or carboxyl group which may be protected;

and $\bigcirc\text{Ar}^1\text{---}$, $\bigcirc\text{Ar}^2\text{---}$, $\bigcirc\text{Ar}^3\text{---}$, $\bigcirc\text{Ar}^4\text{---}$, X^p, Y^p, R^{1p},

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R^{2p}, R^{3p}, R^{4p}, R^{5p}, R⁶, R⁷, R^{8p}, R^{9p}, R^p, p, q and r are as defined above, and, if necessary, removing any protecting group.

- 5 Process 6 is a process for preparing a compound of the formula (gg) wherein A is a group of the formula (b):



wherein R¹², R¹³, p, q and r are as defined above, i.e. a compound of the formula (gg-e).

- 10 The reaction of oxidizing the compound of the formula (IV-e) is usually preferably carried out in an inert solvent by using so-called Dess-Martin oxidation employing 12-I-5 triacetoxyperiodinane; so-called Swern oxidation employing oxalyl chloride and dimethyl sulfoxide; a sulfur trioxide-pyridine complex; pyridinium
15 chlorochromate; active manganese dioxide; or tetra-n-propylammonium perruthenate.

- The inert solvent may, for example, be a halogenated hydrocarbon such as methylene chloride, chloroform or dichloroethane; an ether such as ethyl ether, tetrahydrofuran or dioxane; an aprotic
20 polar solvent such as acetonitrile, acetone, ethyl acetate or dimethyl sulfoxide; or a mixture of such solvents.

- The reaction temperature varies depending upon the type of the oxidizing agent, etc. However, it is usually from -100°C to the boiling point of the solvent used for the reaction, preferably from -70°C
25 to 100°C.

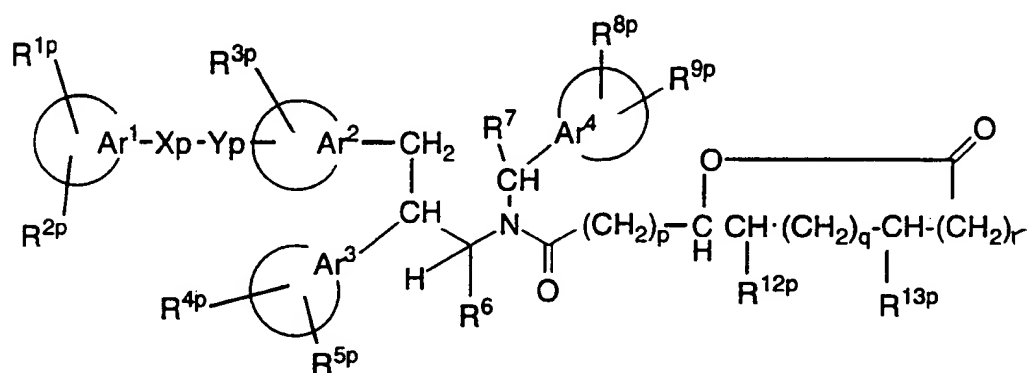
The reaction time is usually from 5 minutes to 7 days, preferably from 10 minutes to 24 hours.

- After completion of the reaction, the product is subjected to usual treatment after removing a protecting group when such a
30 protecting group is present, or directly when no such protecting group is present, to obtain the compound of the formula (gg-e).

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The removal of the protecting group and the post-treatment may be conducted in the same manner as described above with respect to process 1.

- Further, a compound corresponding to the compound of the formula (IV-e) to be used as the starting material in the above process 6, can be prepared, for example, by hydrolyzing a compound of the formula (IV-e-1):



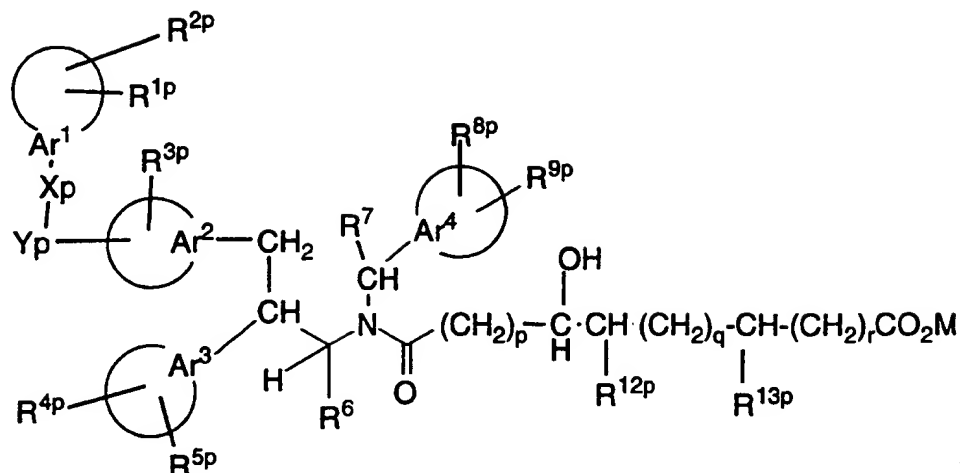
(IV-e-1)

10

wherein $\bigcirc\text{Ar}^1$ —, $\bigcirc\text{Ar}^2$ —, $\bigcirc\text{Ar}^3$ —, $\bigcirc\text{Ar}^4$ —, XP, YP, R^{1p}, R^{2p}, R^{3p}, R^{4p}, R^{5p}, R⁶, R⁷, R^{8p}, R^{9p}, R^{12p}, R^{13p}, p, q and r are as defined above, in the presence of a base, to obtain a compound of the formula (IV-e-2),

15

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(IV-c-2)

wherein M is a hydrogen atom or an alkali metal

5 atom; and Ar^1 —, Ar^2 —, Ar^3 —, Ar^4 —, Xp , Yp , R^{1p} , R^{2p} , R^{3p} , R^{4p} , R^{5p} , R^6 , R^7 , R^{8p} , R^{9p} , R^{12p} , R^{13p} , p , q and r are as defined above, then reacting thereto a diazo compound of the formula

10 $\text{RPP} - \text{N}^+ \equiv \text{N}$

wherein RPP is a lower alkyl group, a lower alkenyl group, an aralkyl group or a lower alkoxycarbonylalkyl group, or an alkylating agent of the formula $\text{RPP}-\text{Z}^1$, wherein RPP and Z^1 are as defined above.

15 Isolation and purification of the compound of the formula (gg), (gg-a), (gg-b), (gg-c), (gg-d) or (gg-e), obtained by the above process can be conducted by a single use or a proper combination of conventional separating means such as column chromatography employing silica gel, adsorbent resin, etc., liquid chromatography,
20 solvent extraction and recrystallization-precipitation.

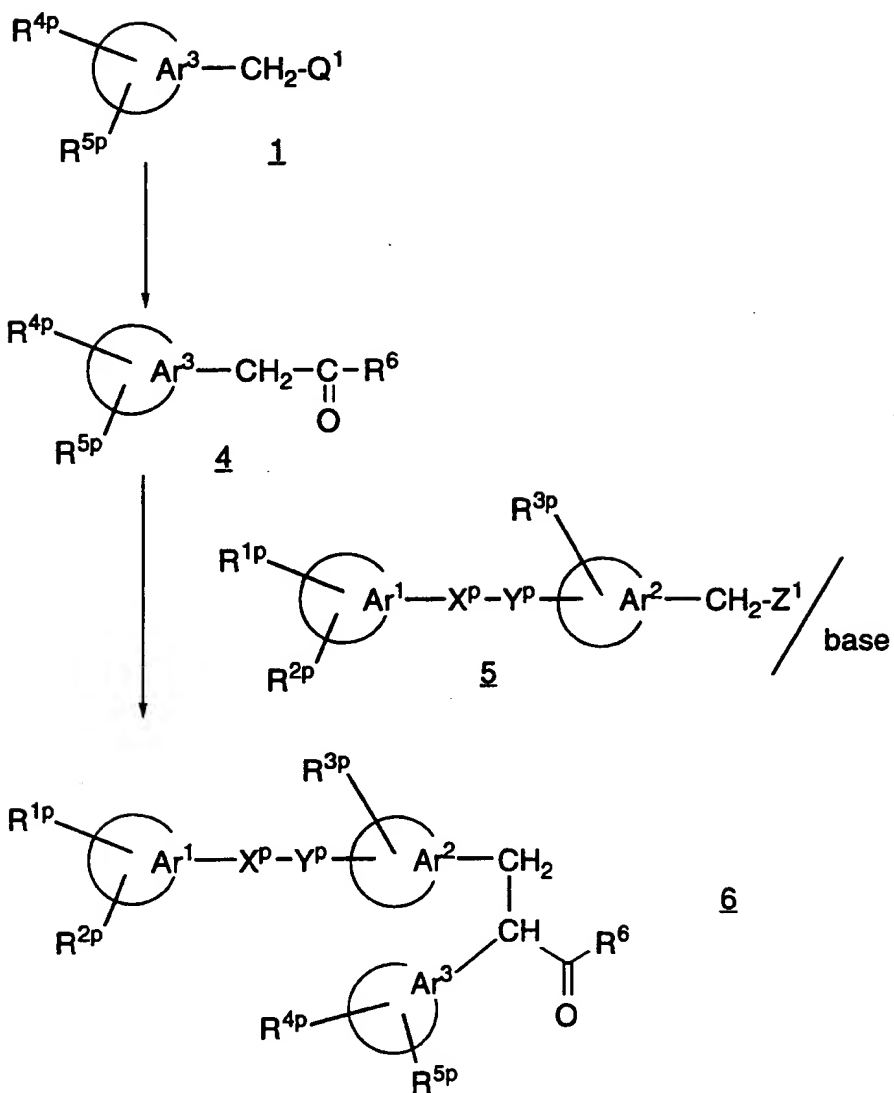
The compound of the formula (gg), (gg-a), (gg-b), (gg-c), (gg-d) or (gg-e) can be converted to a pharmaceutically acceptable salt or ester by a conventional method. Conversely, the conversion from the

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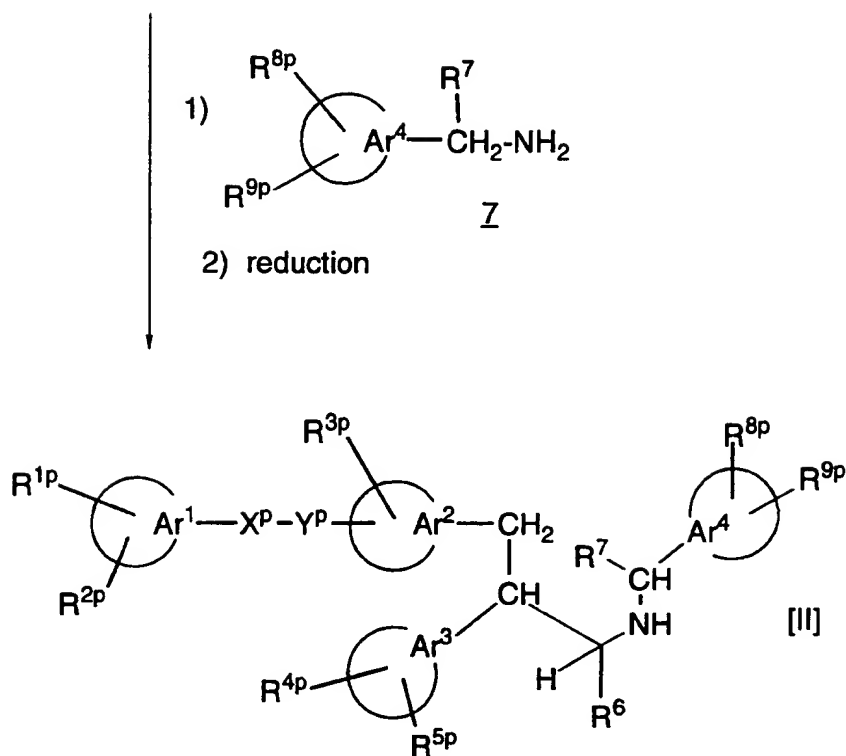
salt or ester to a free carboxylic acid can also be conducted by a conventional method.

The compounds of the formulas (II), (III), (V), (VI), (VII), (VIII), (IX), (X), (XII) and (XIII) may be commercially available or
5 can be prepared in accordance with the methods disclosed in literatures (J. Med. Chem., 10, 717 (1967); *ibid.*, 725; J. Chem. Soc. Perkin I, 1636 (1978); Chem. Lett., 191 (1980); *ibid.*, 375 (1984); J. Chem. Soc. Chem. Commun., 579 (1984); J. Am. Chem. Soc., 104, 5716 (1982)) or
10 methods similar thereto, or in accordance with the following processes or the methods disclosed in Examples.

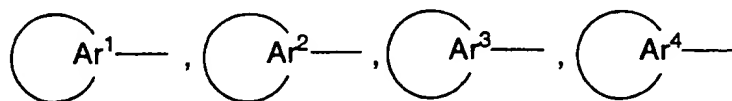
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Process A

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In the above formulas, Q^1 is a cyano group, a carboxyl group, a lower alkoxy carbonyl group, a chloroformyl group or an N-methoxy-N-methylcarbamoyl group; Q^2 is a halogen atom; Z^1 is a leaving group selected from the group consisting of a chlorine atom, a bromine atom, an iodine atom, a trifluoroacetoxy group, a methanesulfonyloxy group, a trifluoromethanesulfonyloxy group and a p-toluenesulfonyloxy group; and



X^p, Y^p,

R^{1p}, R^{2p}, R^{3p}, R^{4p}, R^{5p}, R⁶, R⁷, R^{8p}, R^{9p} are as defined above.

By this process, the desired compound (II) can be prepared by reacting a nitrile or a carboxylic acid derivative of the formula 1 with an alkyl lithium of the formula 2 or an alkyl Grignard reagent (or an alkyl Gilman reagent) of the formula 3 to obtain a ketone compound 4, then reacting an alkylating agent of the formula 5 to the ketone

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compound 4 to produce a compound of the formula 6, then reacting the compound 6 with an amine compound of the formula 7, followed by reduction.

5 The above reaction steps will be described in detail referring to suitable reaction conditions, etc.

10 The first step of preparing the ketone compound 4 is conducted usually by reacting 1 mol or an excess molar amount, preferably from 1 to 5 mols of the alkyl lithium reagent 2 or the alkyl Grignard reagent (or the alkyl Gilman reagent in the case where the
10 substituent Q¹ of the compound 1 is a chloroformyl group) 3 to 1 mol of the starting material compound 1 in a solvent inert to the reaction such as tetrahydrofuran, ethyl ether or benzene, if necessary followed by hydrolysis under an acidic condition.

15 The reaction temperature is usually from -80°C to the boiling point of the solvent used for the reaction, preferably from -70°C to 50°C. The reaction time is usually from 5 minutes to 48 hours, preferably from 30 minutes to 24 hours.

20 When the substituent Q¹ in the formula of the starting material compound 1 is a cyano group, it may be necessary to conduct a hydrolytic reaction under an acidic condition after completion of the reaction, and such a hydrolytic reaction is conducted in e.g. methanol, ethanol, tetrahydrofuran or a solvent mixture thereof with water in the presence of an acid such as hydrochloric acid, sulfuric acid or p-toluenesulfonic acid.

25 The reaction temperature is usually from 0°C to the boiling point of the solvent used for the reaction, and the reaction time is from 30 minutes to 24 hours.

30 The step of preparing the compound of the formula 6 from the ketone compound 4, can be conducted by reacting an equimolar amount or an excess molar amount, preferably from 1 to 2 mols, of the alkylating agent of the formula 5 to the ketone compound 4 in the presence of a base in an inert solvent which does not adversely affect the reaction or without using any solvent.

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The inert solvent may, for example, be an ether such as ethyl ether, tetrahydrofuran or dioxane; an aromatic hydrocarbon such as benzene, toluene or xylene; an aprotic polar solvent such as dimethylformamide, dimethyl sulfoxide or hexamethylphosphoric triamide, or a mixture of such solvents.

The base to be used for this reaction, may, for example, be an alkali metal hydride such as sodium hydride, lithium hydride or potassium hydride; a lithium amide such as lithium amide, lithium diisopropylamide or lithium bis(trimethylsilyl)amide; an alkyl lithium such as methyl lithium, butyl lithium or tert-butyl lithium; an alkali metal alkoxide such as sodium methoxide, sodium ethoxide or potassium tert-butoxide; or an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide.

The base is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the starting material alkylating agent 5.

The reaction temperature is usually from -100°C to the boiling point of the solvent used for the reaction, preferably from -80°C to 100°C. The reaction time is usually from 10 minutes to 48 hours, preferably from 30 minutes to 24 hours.

The step of preparing the desired compound (II) from the compound of the formula 6 can be conducted usually in an inert solvent such as methanol, ethanol, benzene, ethyl ether or tetrahydrofuran by reacting 1 mol or an excess molar amount, preferably from 1 to 2 mols, of the amine compound of the formula 7 to 1 mol of the compound of the formula 6 to preliminarily form an imine, which is subsequently reduced.

The reaction temperature in the process for forming the above imine is usually from 0°C to the boiling point of the solvent used for the reaction, preferably from room temperature to 100°C. The reaction time is usually from 5 minutes to 48 hours, preferably from 30 minutes to 24 hours. After the formation of the imine, the reaction solution may be used as it is to the subsequent step of the reduction reaction, or the reaction solution may be distilled or subjected to a

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conventional separation means to isolate the imine compound, which is then subjected to the subsequent reduction.

The reduction can be carried out by using a metal hydride complex such as sodium borohydride, sodium cyanoborohydride or lithium aluminum hydride, or by catalytic reduction employing a palladium-carbon catalyst or a Raney nickel catalyst.

When a metal hydride complex is used as a reducing agent, the reducing agent is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the above imine.

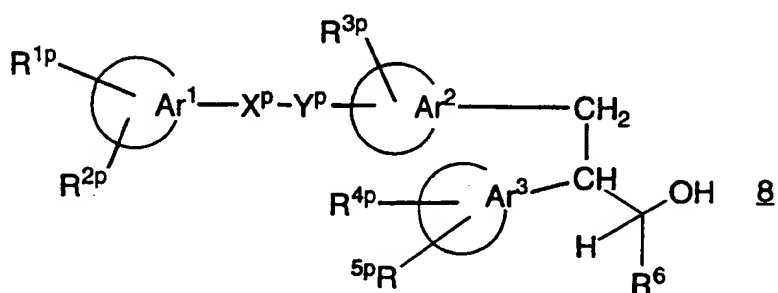
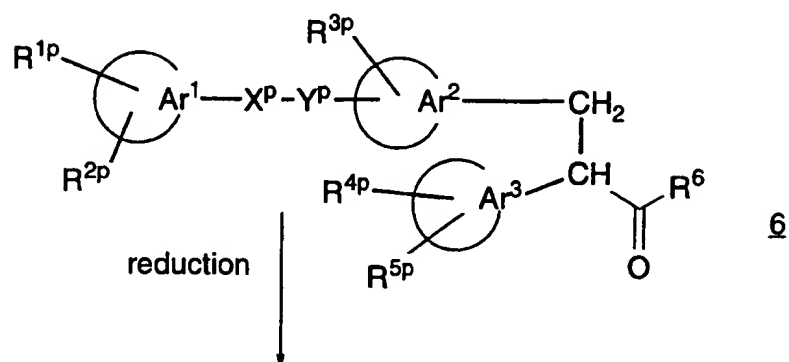
For the reduction, an inert solvent, for example, an alcohol such as methanol or ethanol; an ether such as dimethyl ether, ethyl ether, diisopropyl ether, dibutyl ether, dimethoxyethane, dioxane, tetrahydrofuran or diglyme; an aliphatic hydrocarbon such as pentane, hexane, heptane or cyclohexane; or an aromatic hydrocarbon such as benzene or toluene; or a mixture of such solvents, can be used appropriately as a solvent depending upon the type of the reducing agent.

The reaction temperature is usually from 0°C to room temperature, and the reaction time is usually from 1 hour to 6 hours.

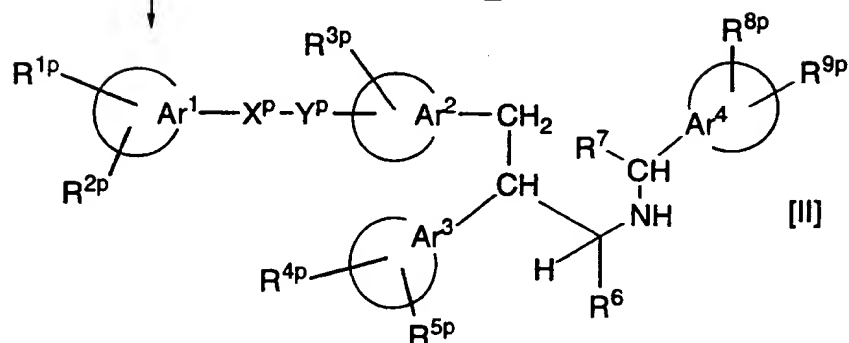
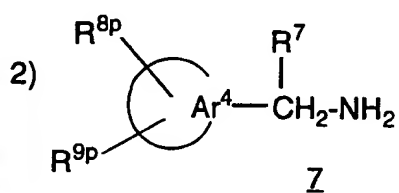
Further, in this process, it is also possible to react an alkylating agent of the formula 5 to the nitrile or carboxylic acid derivative of the formula 1 to preliminarily produce an alkyl compound and then to react an alkyl lithium of the formula 2 or an alkyl Grignard reagent (or an alkyl Gilman reagent) of the formula 3 to the alkyl compound to obtain a compound of the formula 6. Such a reaction can be conducted under the conditions similar to the above Process A. Accordingly, the reaction conditions described for the above Process A may all be used as the reaction conditions for this reaction.

The compounds of the formulas 1, 2, 3, 5 and 7 may be commercially available or can be produced by a proper combination, as the case requires, of the methods disclosed in Examples, or conventional methods or methods similar thereto.

Process B

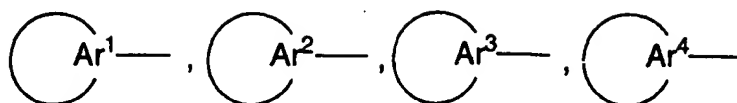


1) $\text{CH}_3\text{SO}_2\text{Cl}/\text{TEA}$ (or PBr_3)



5 In the above formulas,

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XP, Yp, R¹p,
R²p, R³p, R⁴p, R⁵p, R⁶, R⁷, R⁸p and R⁹p are as defined above.

According to this process, the desired compound (II) can be
5 prepared by reacting a reducing agent such as a metal hydride complex
to a compound of the formula 6 to obtain an alcohol compound 8 and
reacting an amine compound of the formula 7 to the alcohol compound
8.

The above reaction steps will be described in detail
10 referring to suitable reaction conditions, etc.

The reaction for reducing the compound of the formula 6
to the alcohol compound 8 can be conducted usually by using a metal
hydride complex such as sodium borohydride, diisobutyl aluminum
hydride, lithium aluminum hydride or lithium tri-sec-butylborohydride
15 (L-selectride™), or by catalytic reduction employing e.g. a palladium-
carbon catalyst or a Raney nickel catalyst, in an inert solvent which does
not adversely affect the reaction.

When the metal hydride complex is used as the reducing
agent, such a reducing agent is used usually in an amount of 1 mol or an
20 excess molar amount, preferably from 1 to 5 mols, per mol of the
starting material compound 6.

The inert solvent to be used in this reaction may be suitably
selected depending upon the type of the reducing agent.

For example, when the reducing agent is sodium
25 borohydride, an inert solvent, such as an alcohol such as methanol or
ethanol; an ether such as dimethoxyethane, dioxane, tetrahydrofuran or
diglyme; an aprotic polar solvent such as dimethylformamide or
dimethylacetamide, or water, or a solvent mixture thereof, may be used,
and particularly preferred is an alcohol such as methanol or ethanol.

30 For example, when the reducing agent is diisobutyl
aluminum hydride, an inert solvent, such as an ether such as dimethyl
ether, ethyl ether, diisopropyl ether, dibutyl ether, dimethoxyethane,

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dioxane, tetrahydrofuran or diglyme; an aliphatic hydrocarbon such as pentane, hexane, heptane or cyclohexane; an aromatic hydrocarbon such as benzene or toluene; methylene chloride, or a solvent mixture thereof may be used, and particularly preferred is toluene or methylene chloride.

For example, when the reducing agent is lithium aluminum hydride or lithium tri-sec-butylborohydride, an inert solvent, such as an ether such as dimethyl ether, ethyl ether, diisopropyl ether, dibutyl ether, dimethoxyethane, dioxane, tetrahydrofuran or diglyme; an aliphatic hydrocarbon such as pentane, hexane, heptane or cyclohexane; or an aromatic hydrocarbon such as benzene or toluene, or a solvent mixture thereof, may be used, and particularly preferred is ethyl ether or tetrahydrofuran.

For the catalytic reduction, the solvent is preferably an alcohol such as methanol or ethanol.

The reaction temperature and the reaction time vary depending upon the stability and the susceptibility to the reduction reaction of the starting material ketone compound 6, the type of the reducing agent and the type of the solvent. However, the reaction temperature is usually from -80°C to 100°C, preferably from -70°C to 40°C, and the reaction time is usually from 5 minutes to 2 days, preferably from 30 minutes to 24 hours.

The step of preparing the desired compound (II) from a compound of the formula 8 can be carried out by reacting a sulfonating agent such as methanesulfonyl chloride to the alcohol compound of the formula 8 in the presence of a base, or reacting a halogenating agent such as thionyl chloride or phosphorous tribromide thereto, to convert the hydroxyl group in the formula to a leaving group, followed by reacting an amine compound of the formula 7.

The reaction for introducing the leaving group can be conducted usually by reacting 1 mol or an excess molar amount, preferably from 1 to 2 mols, of a sulfonating agent and a base such as triethylamine to 1 mol of the alcohol compound 8 in an inert solvent such as methylene chloride, chloroform, benzene, tetrahydrofuran or

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ethyl acetate, or using 1 mol or an excess molar amount, preferably from 1 to 5 mols, of a halogenating agent.

The reaction temperature is usually from -70°C to the boiling point of the solvent used for the reaction, preferably from -20°C to 80°C, and the reaction time is usually from 5 minutes to 48 hours, preferably from 30 minutes to 24 hours.

Then, the step of reacting an amine compound 7 to the compound having the leaving group introduced, obtained by the above reaction, can be conducted usually by employing 1 mol or an excess molar amount, preferably from 1 to 50 mols, of the amine compound 7 per mol of the starting compound having the leaving group, in an inert solvent such as methylene chloride, chloroform, benzene, ethyl ether or tetrahydrofuran.

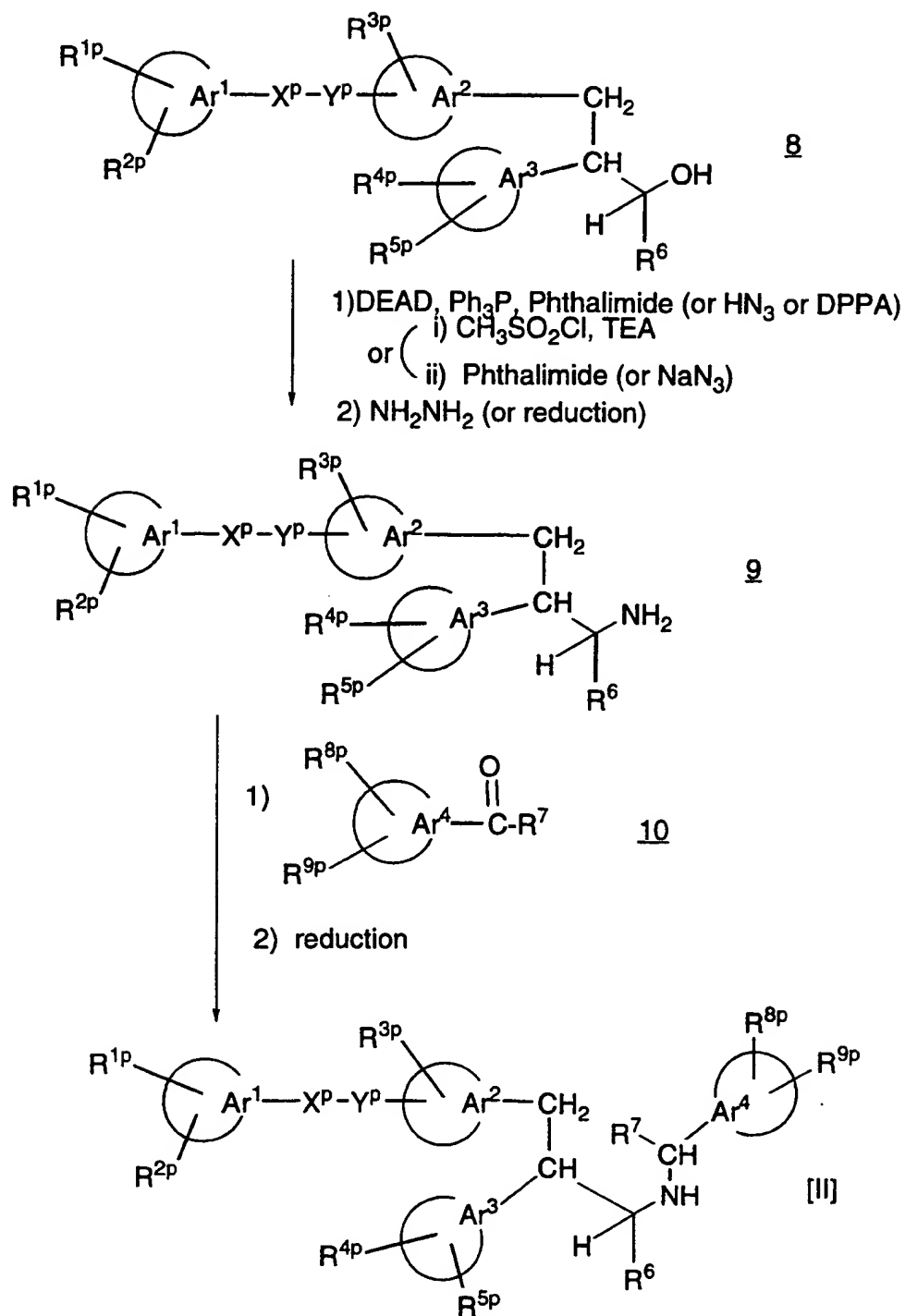
If necessary, this reaction can be conducted in the presence of a base other than the amine compound of the formula 7.

As such a base, an inorganic base such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate or sodium hydrogencarbonate, or an organic base such as triethylamine, N-ethyldiisopropylamine, pyridine or N,N-dimethylaniline may, for example, be mentioned.

Such a base is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the starting material compound.

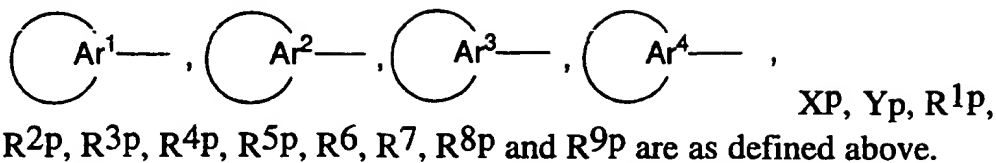
The reaction temperature is usually from -50°C to 150°C, preferably from -20°C to 100°C, and the reaction time is usually from 5 minutes to 7 days, preferably from 10 minutes to 24 hours.

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Process C

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In the above formulas,



- According to this process, the desired compound (II) can be prepared by firstly reacting diethyl azodicarboxylate, triphenylphosphine and phthalimide (or hydrogen azide or diphenylphosphoryl azide) or reacting a sulfonylation agent such as methanesulfonyl chloride in the presence of a base such as triethylamine, then reacting phthalimide (or sodium azide) in the presence of a base, to the alcohol compound of the formula 8, to obtain a phthalimide-protected form (or an azide compound) of the amine compound 9, then reacting hydrazine (or a reducing agent) to remove the phthalimide group (or reduce the azide group) to obtain an amine product of the formula 9, and finally reacting a compound of the formula 10 to the compound 9, followed by reduction.

The above reaction steps will be described in detail referring to suitable reaction conditions, etc.

- For the step of producing the amine compound of the formula 9 from the alcohol compound 8, various synthetic methods and reaction conditions well known in organic synthetic chemistry for converting alcohol compounds to amines, may be employed. For example, it is preferred to employ a Mitsunobu reaction using diethyl azodicarboxylate, triphenylphosphine and phthalimide (or hydrogen azide or diphenylphosphoryl azide) or a method which comprises sulfonylation with a sulfonylation agent such as methanesulfonyl chloride in the presence of a base such as triethylamine, then reacting phthalimide (or sodium azide) in the presence of a base, and then treating the obtained phthalimide compound with hydrazine (or reducing the azide compound).

- The above reactions are conducted usually in a solvent inert to the reaction. The inert solvent may, for example, preferably be tetrahydrofuran, dimethoxyethane, benzene or toluene in the case of the above-mentioned Mitsunobu reaction; methylene chloride, chloroform,

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5 tetrahydrofuran, benzene, ethyl acetate or dimethylformamide in the case of the sulfonylation followed by the reaction with phthalimide (or sodium azide); an alcohol such as methanol or ethanol in the next step of the phthalimide-removing reaction with hydrazine; an ether such as
10 ethyl ether or tetrahydrofuran in the case where a metal hydride complex is used as the reducing agent in the reduction reaction of the azide compound; water-containing tetrahydrofuran in the case where phosphine reduction is conducted with triphenylphosphine or the like; and an alcohol such as methanol or ethanol in the reduction by catalytic
15 reduction.

With respect to the amounts of the reagents to be used, in the above Mitsunobu reaction, each of diethyl azodicarboxylate, triphenylphosphine and phthalimide (or hydrogen azide or diphenylphosphoryl azide) is used in an amount of 1 mol or an excess
20 molar amount, preferably from 1 to 5 mols, per mol of the starting material alcohol compound 8. In the reaction with the phthalimide (or sodium azide) after the sulfonylation, the sulfonylation agent such as methanesulfonyl chloride is used in an amount of 1 mol or an excess molar amount, preferably from 1 to 2 mols, per mol of the alcohol
25 compound 8, and the base such as triethylamine used at that time is usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 2 mols, per mol of the sulfonylation agent. In the next step of the reaction with phthalimide (or sodium azide) in the presence of a base, 1 mol or an excess molar amount, preferably from 1 to 5 mols of
30 each of phthalimide and the base (or sodium azide) is used per mol of the starting material sulfonylation agent. Here, the base to be used together with phthalimide is preferably sodium carbonate or potassium carbonate. Otherwise, without using such a base, a sodium salt or a potassium salt of phthalimide may be used by itself. Then, in the reaction for removing the phthalimide group with hydrazine, hydrazine is used in an amount of 1 mol or an excess molar amount, preferably from 1 to 10 mols, per mol of the phthalimide compound as the starting material compound. In the reduction of the azide compound with a metal hydride complex or with triphenylphosphine, the reducing agent

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is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 2 mols, per mol of the azide compound.

In the case of the above Mitsunobu reaction, the reaction temperature is usually from -70°C to 100°C , preferably from -20°C to 50°C , and the reaction time is usually from 5 minutes to 48 hours, preferably from 30 minutes to 24 hours. In the reaction for removing the phthalimide group by hydrazine, the reaction temperature is usually from 0°C to the boiling point of the solvent used for the reaction, preferably from room temperature to 100°C , and the reaction time is usually from 5 minutes to 48 hours, preferably from 30 minutes to 24 hours. In the reaction for converting the azide compound to the amine compound by reduction, when a metal hydride complex is used as the reducing agent, the reaction temperature is usually from -70°C to 150°C , preferably from -20°C to 50°C , and the reaction time is usually from 5 minutes to 48 hours, preferably from 10 minutes to 10 hours. When triphenylphosphine is used as the reducing agent, the reaction temperature is usually from room temperature to the boiling point of the solvent used for the reaction, preferably from 30°C to 100°C , and the reaction time is usually from 10 minutes to 48 hours, preferably from 30 minutes to 24 hours. Further, in the case of the reduction by catalytic reduction, the reaction temperature is usually from 0°C to 100°C , preferably from room temperature to 50°C , and the reaction time is usually from 10 minutes to 48 hours, preferably from 10 minutes to 24 hours.

The step for producing the desired compound (II) from the compound of the formula 9 is carried out usually by preliminarily forming an imine by reacting 1 mol or an excess molar amount, preferably from 1 to 2 mols of the compound of the formula 10 to 1 mol of the compound of the formula 9 in an inert solvent such as methanol, ethanol, benzene, ethyl ether or tetrahydrofuran, and then reducing it.

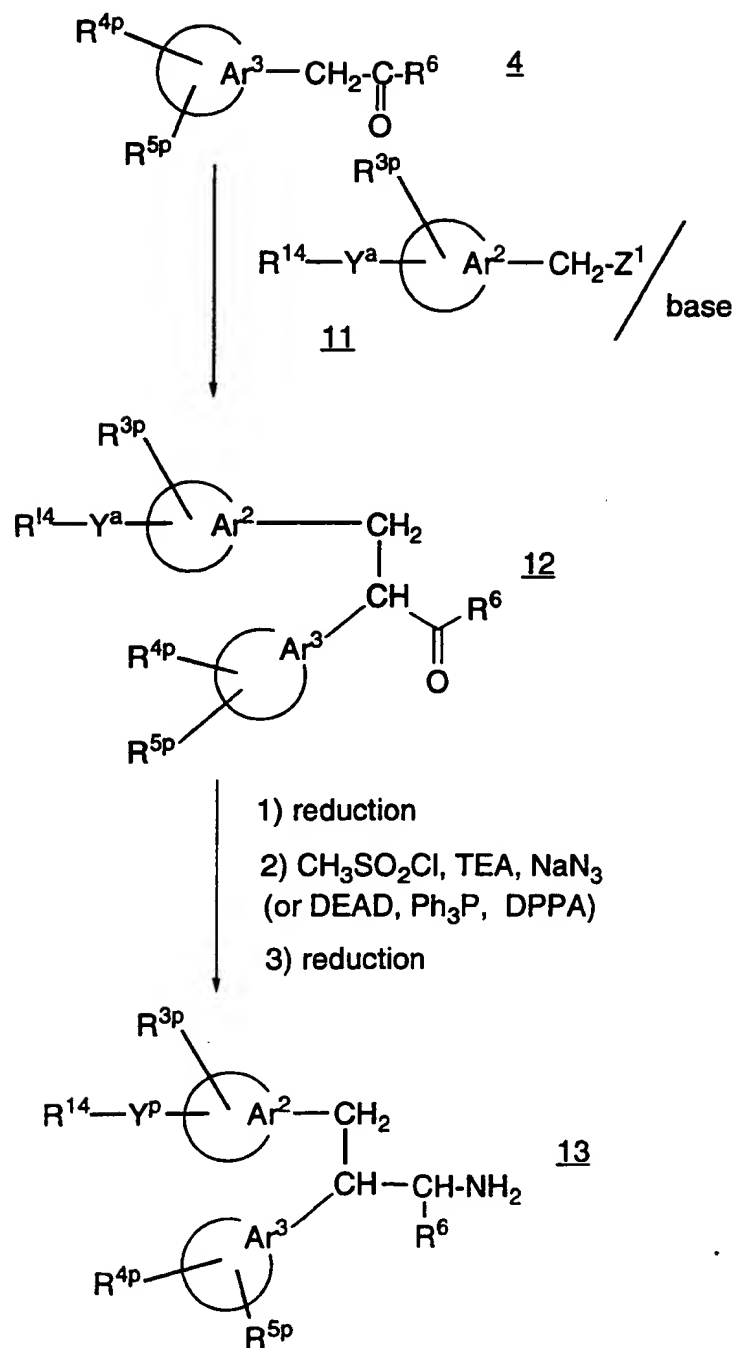
This step can be carried out in the same manner as the step for producing the desired compound (II) from the compound of the

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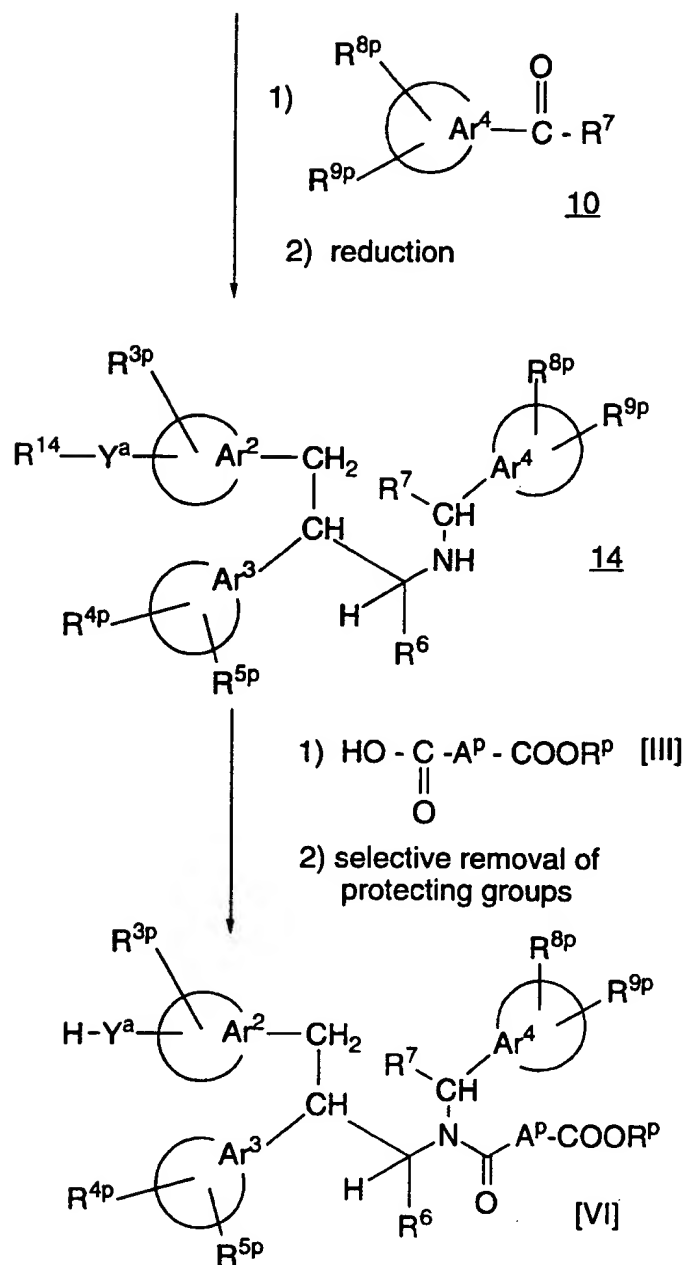
formula 6 in the above process A. Accordingly, with respect to the reaction conditions, etc., similar conditions may be employed.

Further, the compound of the formula 10 may be commercially available or can be produced by a proper combination, as
5 the case requires, of the methods disclosed in Examples, or conventional methods or methods similar thereto.

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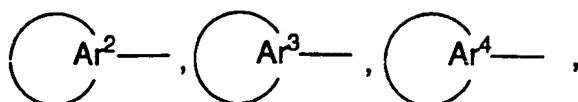
Process D

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- in the above formulas, R^{14} means a hydroxylprotecting group when Y^a is an oxygen atom; a mercapto-protecting group when Y^a is a sulfur atom; or an amino- or imino-protecting group when Y^a is a group of the formula $-\text{NR}^b-$ (wherein R^b is as defined above); and
- 5

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AP, Y^a, Z¹, R^{3p}, R^{4p}, R^{5p}, R⁶, R⁷, R^{8p}, R^{9p} and R^p are as defined above.

- According to this process, the desired compound (VI) can
- 5 be prepared by firstly reacting an alkylating agent of the formula 11 to a ketone compound of the formula 4 to obtain a compound of the formula 12, reacting a reducing agent such as a metal hydride complex to the compound 12 to obtain an alcohol compound, then reacting diethyl azodicarboxylate, triphenylphosphine and phthalimide (or
 - 10 hydrogen azide or diphenylphosphoryl azide) or reacting a sulfonylation agent such as methanesulfonyl chloride in the presence of a base such as triethylamine, and then reacting phthalimide (or sodium azide) in the presence of a base, to obtain a phthalimide-protected form (or an azide compound) of the amine compound 13, then reacting hydrazine (or a
 - 15 reducing agent) to remove the phthalimide group (or reduce the azide group) to obtain an amine compound of the formula 13, reacting a compound of the formula 10 to the compound 13, followed by reduction to obtain a compound of the formula 14, reacting a carboxylic acid of the formula (III) or its reactive derivative to the compound 14, and
 - 20 finally selectively removing the protecting group represented by R¹⁴.

The step of producing a compound of the formula 12 from a ketone compound of the formula 4, can be carried out in the same manner as the step of producing the compound of the formula 6 from the ketone of the formula 4 in the above process A. Accordingly, with

- 25 respect to the reaction conditions, etc., similar conditions may be employed.

When R¹⁴ is a hydroxyl-protecting group, such a hydroxyl-protecting group may be the one disclosed above with respect to process 1.

- 30 When R¹⁴ is a mercapto-protecting group, the hydroxyl-protecting group disclosed above with respect to process 1 can be used as such a mercapto-protecting group.

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When R¹⁴ is an amino- or imino-protecting group, such an amino- or imino-protecting group may be the amino- or imino-protecting group disclosed above with respect to process 1.

5 In the step of producing the amine compound of the formula 13 after reacting a reducing agent such as a metal hydride complex to the compound of the formula 12 to obtain an alcohol compound, the step of converting the compound of the formula 12 to the alcohol compound can be carried out in the same manner as the step of reducing the compound of the formula 6 to the alcohol compound 8
10 in the above process B. Accordingly, with respect to the reaction conditions, etc., similar conditions may be employed. Further, the step of producing an amine compound of the formula 13 from the obtained alcohol, can be carried out in the same manner as in the step of producing the amine compound 9 from the alcohol compound of the formula 8 in the above process C. Accordingly, with respect to the
15 reaction conditions, etc., similar conditions may be employed.

The step of producing a compound of the formula 14 from the amine compound of the formula 13, can be carried out in the same manner as in the step of producing a compound of the formula (II) from
20 the amine of the formula 9 in the above process C. Accordingly, with respect to the reaction conditions, etc., similar conditions may be employed.

In the step of producing the desired compound (VI) from the compound of the formula 14, the reaction of the compound of the
25 formula 14 with the carboxylic acid of the formula (III) or its reactive derivative, can be carried out in the same manner as the reaction of the compound of the formula (II) with the carboxylic acid of (III) or its reactive derivative in the above process 1. Accordingly, with respect to the reaction conditions, etc., similar conditions may be employed.

30 For the step of selectively removing the protective group represented by R¹⁴ from the compound obtained by the above reaction, various methods may suitably be selected depending upon the type and the characteristics of the protecting group. Namely, utilizing the difference in the stability against an acid, a base or reduction between

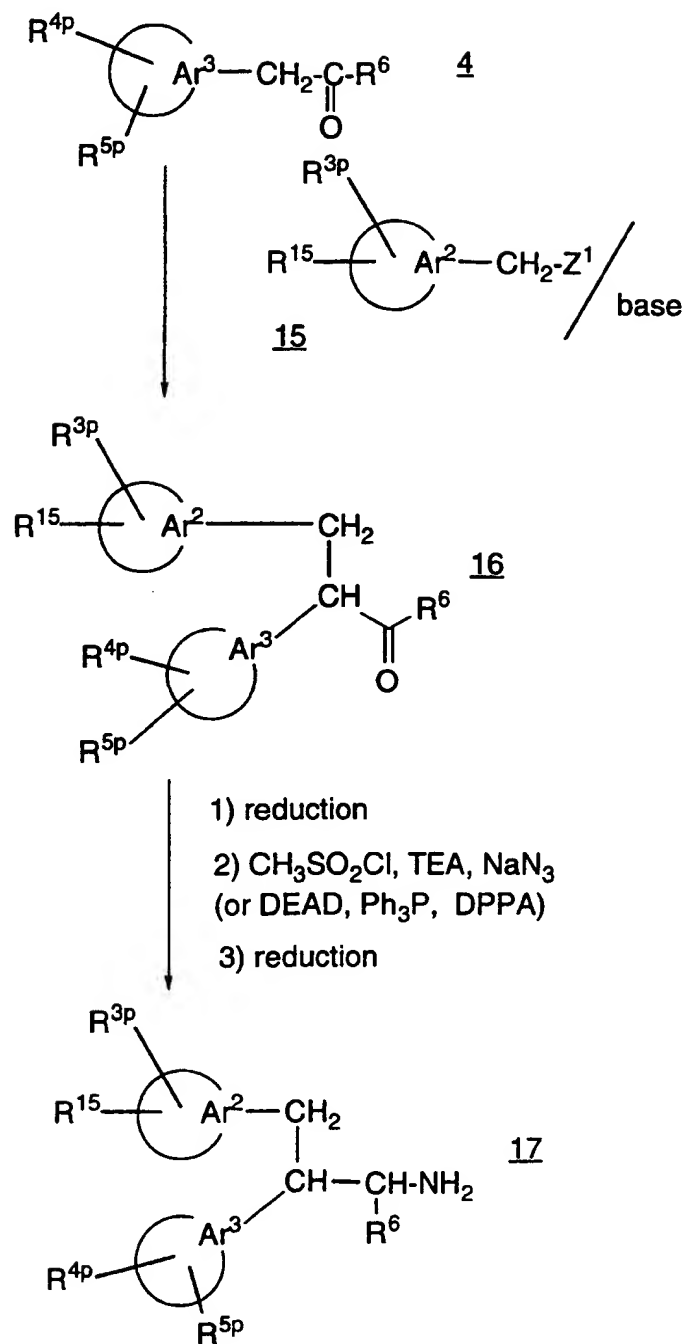
- 260 -

R¹⁴ and other protecting groups, the protecting group can selectively be removed by a conventional means such as an acid, a base or reduction.

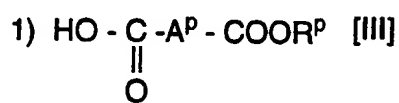
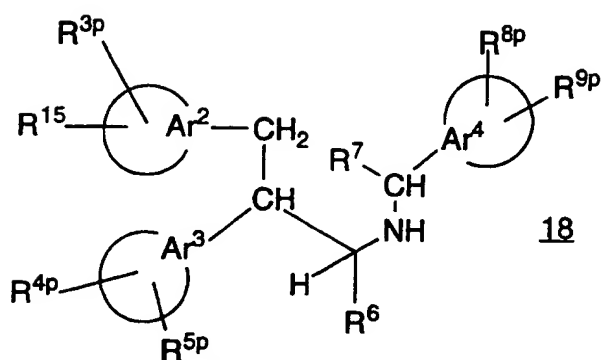
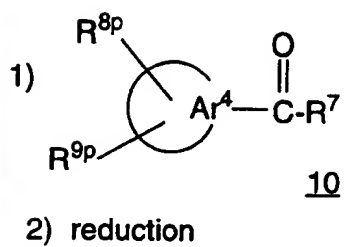
With respect to specific conditions for such a reaction, the methods disclosed in known literatures, such as "Protective Groups in Organic
5 Synthesis, T.W. Greene, John Siley & Sons (1981)", may, for example, be used.

Further, the compound of the formula 11 may be commercially available, or may be produced by a proper combination, as the case requires, of the methods disclosed in Examples, or
10 conventional methods or methods similar thereto.

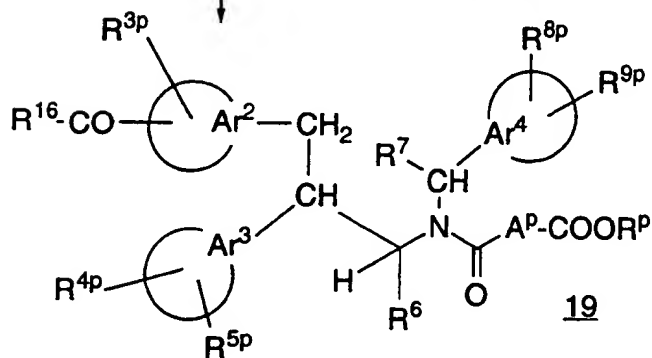
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Process E

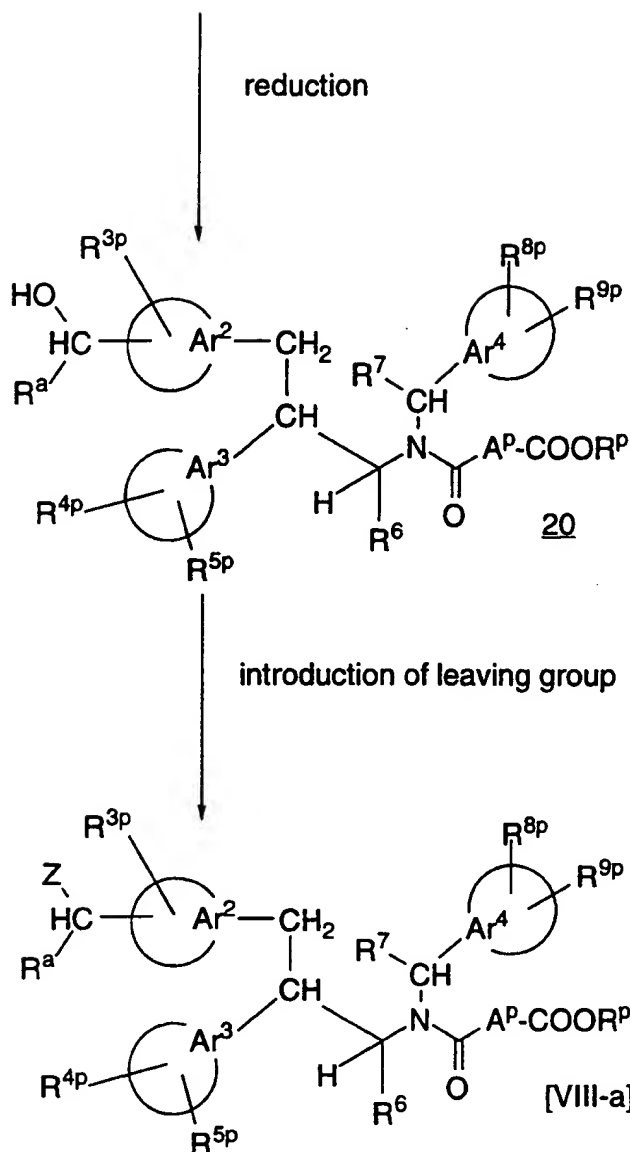
- 262 -



2) selective removal of protecting groups

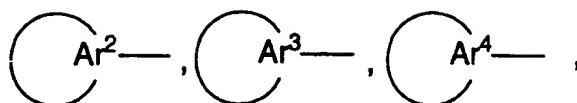


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- In the above formulas, R¹⁵ is a protected carboxyl group or a group of the formula R^a-C(ORP¹)(ORP²)- (wherein each of RP¹ and RP² which are the same or different, is a methyl group or an ethyl group, or RP¹ and RP² together represent an ethylene group, and R^a is as defined above); R¹⁶ is a hydroxyl group or a group of the formula R^a (wherein R^a is as defined above); and
- 5

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AP, Z, Z¹, R³P, R⁴P, R⁵P, R⁶, R⁷, R⁸P, R⁹P, R^a and RP are as defined above.

- According to this process, the desired compound (VIII-a)
- 5 can be prepared by firstly reacting an alkylating agent of the formula 15 to a ketone compound of the formula 4 to obtain a compound of the formula 16, reacting a reducing agent such as a metal hydride complex to the compound 16 to obtain an alcohol compound, then reacting
- 10 diethyl azodicarboxylate, triphenylphosphine and phthalimide (or hydrogen azide or diphenylphosphoryl azide), or reacting a sulfonylation agent such as methanesulfonyl chloride in the presence of a base such as triethylamine and then reacting phthalimide (or sodium azide) in the presence of a base, to obtain a phthalimide-protected form
- 15 (or an azide compound) of the amine compound 17, then reacting hydrazine (or a reducing agent) to remove the phthalimide group (or reduce the azide group) to obtain an amine compound of the formula 17, reacting a compound of the formula 10 to the compound 17, followed by reduction to obtain a compound of the formula 18, reacting
- 20 a carboxylic acid of the formula (III) or its reactive derivative to the compound 18, then selectively removing the protecting group at R¹⁵ to obtain a compound of the formula 19, reacting a reducing agent to the compound 19 to obtain a compound of the formula 20, and finally introducing a leaving group to the compound 20.

- The respective steps up to the production of the compound
- 25 of the formula 19 from the ketone compound of the formula 4 can be carried out in the same manner as the respective steps for the production of the compound of the formula (VI) from the ketone compound of the formula 4 in the above process D. Accordingly, with respect to the reaction conditions, etc., the same conditions as in the corresponding
- 30 respective steps can be employed.

The step of reacting a reducing agent to the compound of the formula 19 to obtain the compound of the formula 20, can be

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conducted in the same manner as the reduction method employing e.g. sodium borohydride as a reducing agent in the step of reducing the compound of the formula 6 to an alcohol compound 8 in the above process B. Accordingly, with respect to the reaction conditions, etc.,
5 similar conditions can be employed.

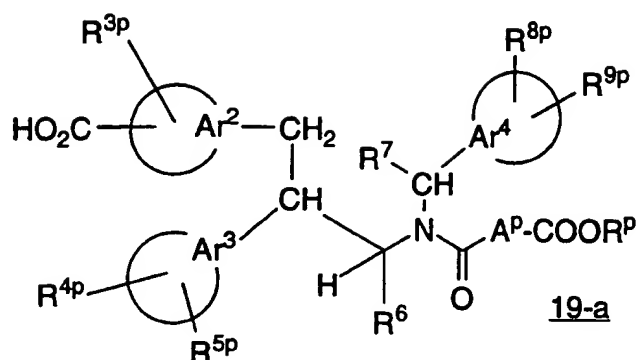
The step of producing the desired compound (VIII-a) by introducing a leaving group to the compound of the formula 20 can be carried out in the same manner as in the method of introducing a leaving group to the compound of the formula 8 in the above process B
10 by using, for example, a halogenating agent such as thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, phosphorus tribromide, oxalyl chloride or phosgene, or a sulfonating agent such as methanesulfonyl chloride, p-toluenesulfonyl chloride or benzenesulfonyl chloride. Accordingly, with respect to the
15 reaction conditions, etc., similar conditions may be employed.

Further, the compound of the formula 15 may be commercially available, or can be produced by a proper combination, as the case requires, of the methods disclosed in Examples, or conventional methods or methods similar thereto.

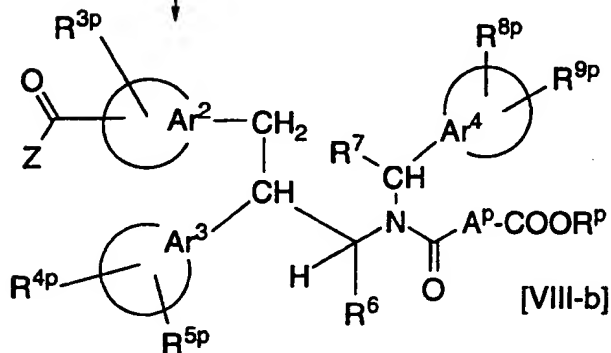
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Process F

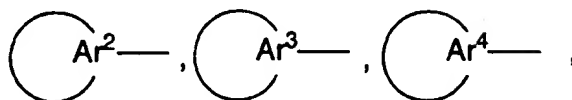
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introduction of leaving group



In the above formulas,



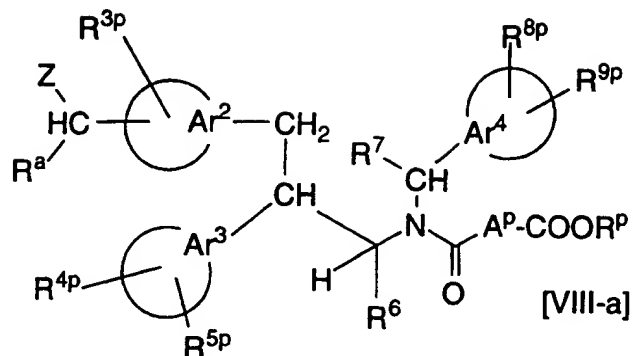
- 5 A^p , Z, R^{3p} , R^{4p} , R^{5p} , R^6 , R^7 , R^{8p} , R^{9p} and R^p are as defined above.

According to this process, the desired compound (VIII-b) can be prepared by introducing a leaving group to the compound of the formula 19-a in the same manner and conditions as the method of introducing a leaving group to the compound of the formula 20 in the

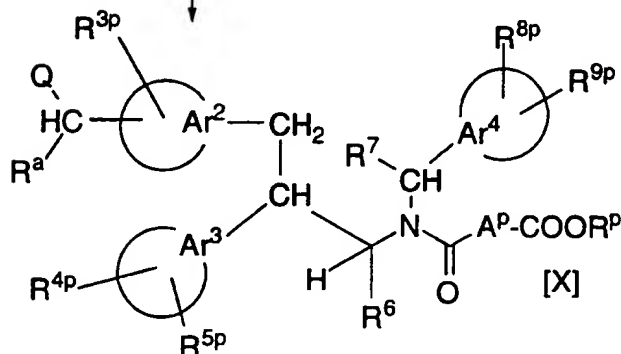
10 above process E.

Process G

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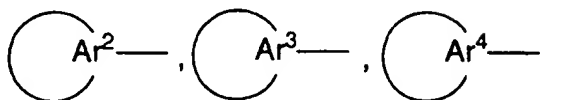


PPh₃ or P(OMe)₃ or P(OEt)₃



In the above formulas,

5



AP, Q, Z, R^{3p}, R^{4p}, R^{5p}, R⁶, R⁷, R^{8p}, R^{9p}, R^a and R^p are as defined above.

10

According to this process, the desired compound (X) can be prepared by reacting triphenylphosphine, trimethyl phosphite or triethyl phosphite, to the compound of the formula (VIII-a).

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When a triphenylphosphine is reacted, the above reaction is carried out usually in an inert solvent which does not affect the reaction. As such an inert solvent, toluene or xylene is, for example, preferred.

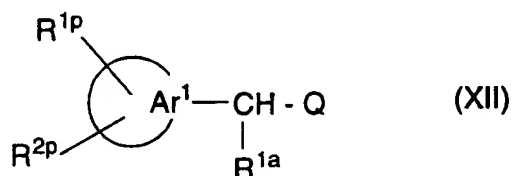
The triphenylphosphine is used usually in an amount of 1
 5 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the compound (VIII-a).

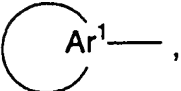
The reaction temperature is usually from room temperature to the boiling point of the solvent used for the reaction, preferably from 80°C to 150°C. The reaction time is usually from 5 minutes to 7 days,
 10 preferably from 1 hour to 24 hours.

Likewise, when trimethyl phosphite or triethyl phosphite is reacted to the compound (VIII-a), the above reaction is conducted usually in an inert solvent which does not affect the reaction, or more preferably, an excess trimethyl phosphite or triethyl phosphite is used as
 15 both the solvent and the reactant.

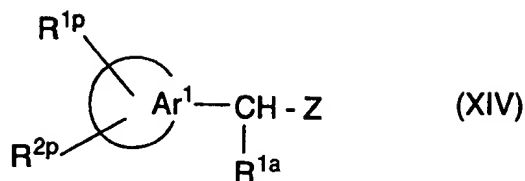
The reaction temperature is usually from room temperature to the boiling point of the solvent for the reaction, preferably from 80°C to 150°C, and the reaction time is usually from 5 minutes to 7 days, preferably from 1 hour to 24 hours.


20 A compound of the formula (XII):



25 wherein , Q, R^{1p}, R^{2p} and R^{1a} are as defined above, can be prepared from a compound of the formula (XIV):

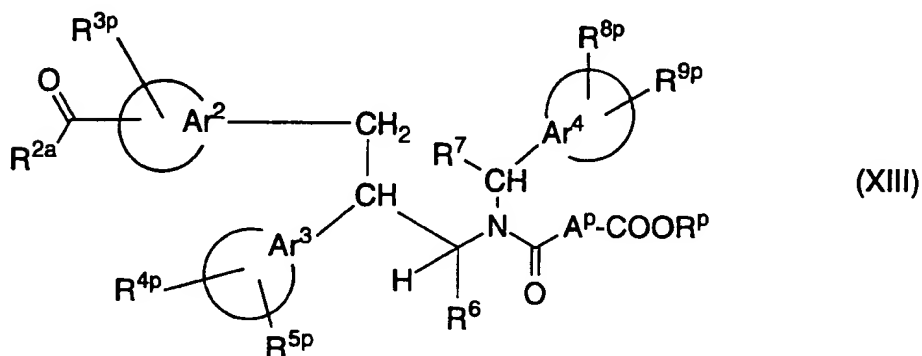
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wherein  Z, R^{1p}, R^{2p} and R^{1a} are as defined above, in accordance with process G.

5 Further, the compound of the formula (XIV) may be commercially available, or can be prepared by a proper combination, as the case requires, of the methods disclosed in Examples, or conventional methods or methods similar thereto.

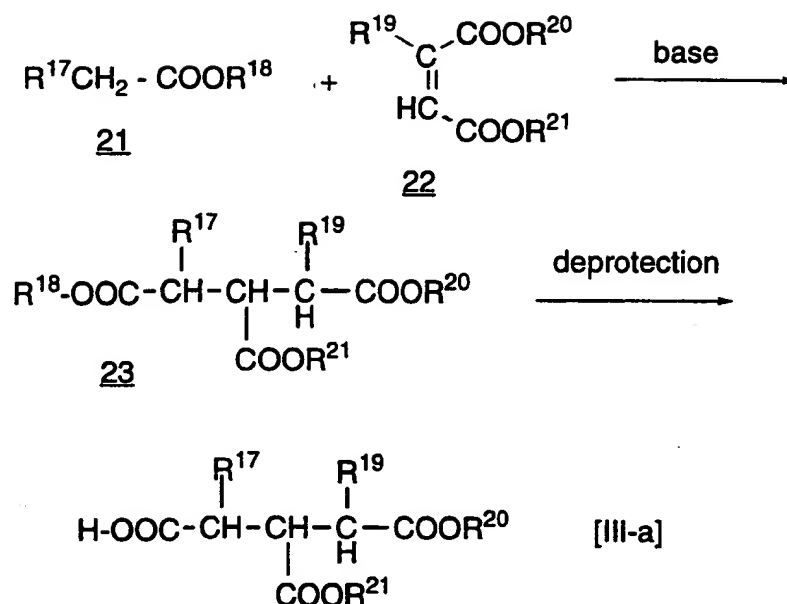
Further, the formula (XIII):



wherein $\bigcirc\text{Ar}^2\text{---}$, $\bigcirc\text{Ar}^3\text{---}$, $\bigcirc\text{Ar}^4\text{---}$, AP, R^{3p}, R^{4p}, R^{5p}, R⁶, R⁷, R^{8p}, R^{9p}, RP and R^{2a} are as defined above, is

15 substantially the same as the formula 19 in the above process E, wherein R¹⁶ is a group of the formula R^a. Accordingly, the compound of the formula (XIII) can be prepared by the above process E.

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Process H

5 In the above formulas, each of R¹⁷ and R¹⁹ which are the same or different, is a hydrogen atom, a lower alkyl group, an aryl group or an aralkyl group; each of R²⁰ and R²¹ which are the same or different, is a carboxyl-protecting group; and R¹⁸ is a tert-butyl group, a benzyl group, a benzhydryl group or a trityl group.

10 Process H is a process for preparing a carboxylic acid derivative of the formula (III-a) among the compounds of the above formula (III).

According to this process, the desired carboxylic acid derivative (III-a) can be prepared by conducting a so-called Michael addition reaction which comprises reacting a maleic acid derivative or a fumaric acid derivative of the formula 22 to an ester derivative having a readily removable carboxyl-protecting group R¹⁸, represented by the formula 21, in the presence of a base, and then removing the carboxyl-protecting group R¹⁸ from the obtained Michael addition product 23 under a mild condition.

As the carboxyl-protecting group for R²⁰ and R²¹, a

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lower alkyl group such as a tert-butyl group, or a benzhydryl group, is preferred.

5 The protecting group R¹⁸ is preferably the one which can readily be removed under a mild condition of catalytic reduction or weakly acidic condition and which is stable under the Michael addition reaction condition, such as a tert-butyl group, a benzyl group, a benzhydryl group or a trityl group.

10 The above Michael addition reaction can be conducted by reacting the compound of the formula 22 in an amount of 1 mol or an excess molar amount, preferably from 1 to 2 mols, to 1 mol of the compound of the formula 21 in the presence of a base such as sodium hydride, butyl lithium, lithium diisopropylamide or lithium bis(trimethylsilyl)amide usually in an inert solvent such as benzene, ethyl ether or tetrahydrofuran.

15 Such a base is used-usually in an amount of 1 mol or a slightly excess molar amount, preferably from 1 to 1.5 mols, per mol of the compound of the formula 22.

20 The reaction temperature is usually from -100°C to 100°C, preferably from -80°C to room temperature, and the reaction time is usually from 5 minutes to 24 hours, preferably from 10 minutes to 10 hours.

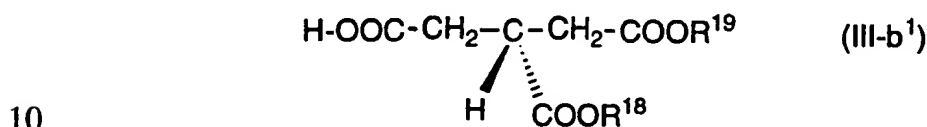
25 The reaction conditions for the reaction for removing the protecting group from the compound of the formula 23 to form the desired carboxylic acid derivative (III-a), vary depending upon the type of the protecting group, etc. For example, when the protecting group is a tert-butyl group, a benzhydryl group or a trityl group, a method may be employed wherein the compound is treated with an acid such as acetic acid, formic acid, trifluoroacetic acid or hydrochloric acid, preferably within a temperature range of from -20°C to 50°C for from 10 minutes to 24 hours in the absence of a solvent or usually in an inert solvent such as methylene chloride, anisole, tetrahydrofuran, methanol or ethanol or a solvent mixture thereof with water.

30 For example, when the protecting group is a benzyl group, a benzhydryl group or a trityl group, a method may be employed

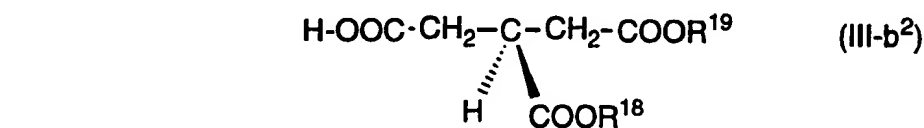
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wherein the compound is catalytically reduced with a catalyst such as a palladium-carbon catalyst or a Raney nickel catalyst preferably under a hydrogen pressure of from 1 to 20 kg/cm² preferably within a temperature range of from 0°C to 40°C for from 10 minutes to 24 hours usually in an inert solvent such as methanol, ethanol, dioxane, water or acetic acid, or a solvent mixture thereof.

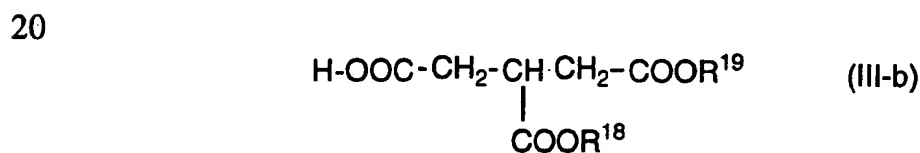
Among compounds of the formula (III-a), an optically active compound of the formula (III-b¹):



or the formula (III-b²):



wherein each of R¹⁸ and R¹⁹ which are the same or different, is a carboxyl-protecting group, can be obtained by reacting a racemic mixture of the compound of the formula (III-b):



wherein R¹⁸ and R¹⁹ are as defined above, with cinchonidine or quinine to obtain a mixture of two diastereomers, then separating and collecting either one of the diastereomers by utilizing the difference in the solubility as between the two diastereomers, followed by recovering the free carboxylic acid by treating with an acid.

Separation of the diastereomer mixture may be conducted in an organic solvent such as carbon tetrachloride or isopropyl ether. Usually, the mixture of the diastereomers is dissolved in a solvent in a

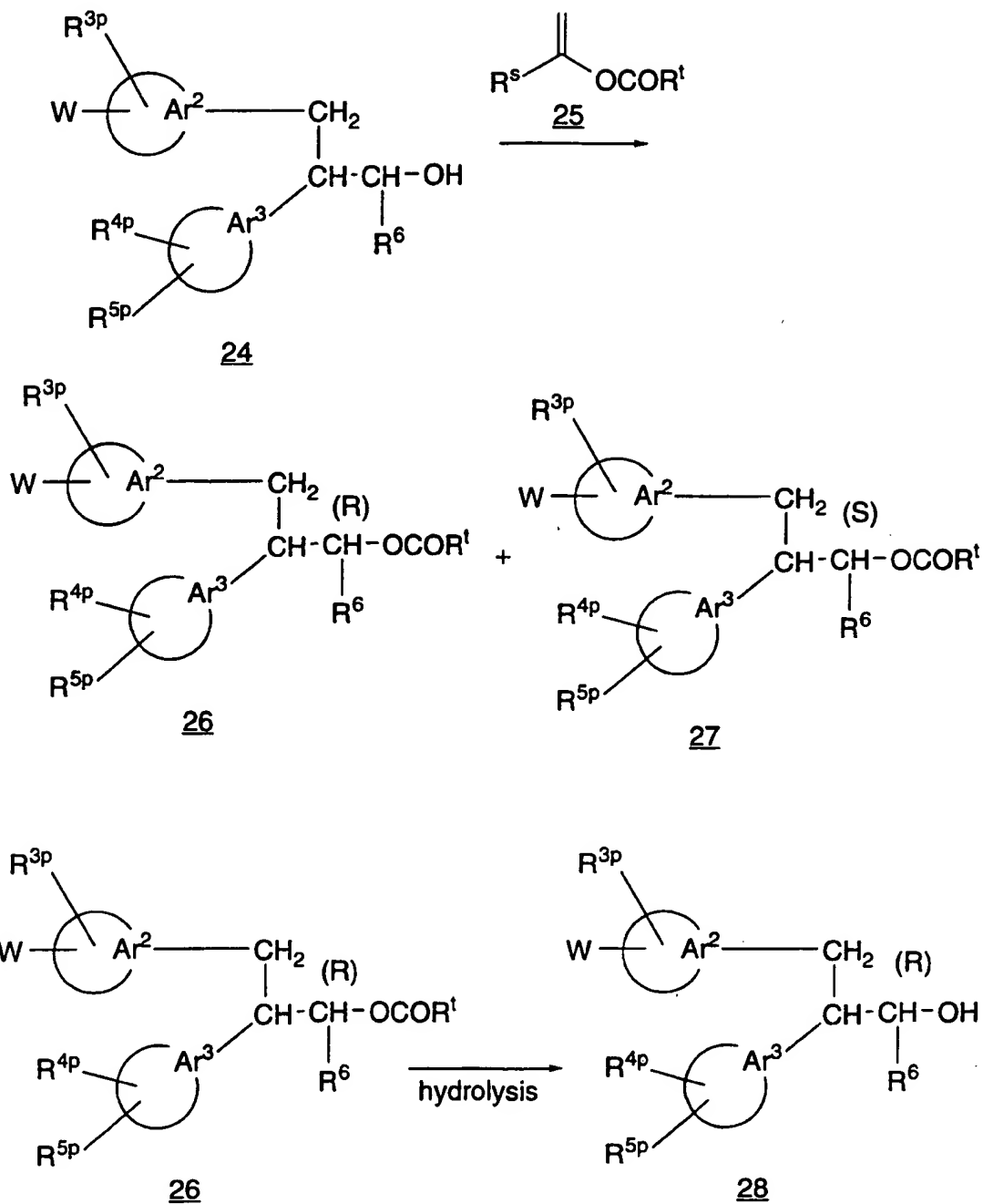
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hot state, and the solution is gradually cooled to utilize the solubility difference for separation of the diastereomers.

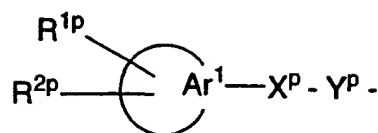
Further, either one of the diastereomers thus obtained is treated with an acid such as hydrochloric acid to obtain an optically
5 active compound of the formula (III-b¹) or (III-b²).

The compounds of the formula 21 and 22 may be commercially available or can be produced by a proper combination, as the case requires, of the methods disclosed in Examples, or conventional
10 methods or methods similar thereto.

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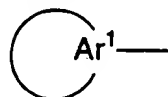
Process I

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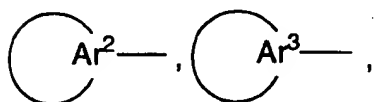


In the above formulas, W is

(wherein



, X^p , Y^p , R^{1p} and R^{2p} are as defined above), R^{14} - Y^a (wherein Y^a and R^{14} are as defined above) or R^{15} (wherein R^{15} is as defined above); R^s is a hydrogen atom or a methyl group; R^t is a lower alkyl group, an aryl group or a lower alkenyl group; and



, R^{3p} , R^{4p} , R^{5p} and R^6 are as defined above.

Process I is a process for preparing an optically active substance 27 or 28 of an alcohol compound 24 obtainable as the above formula 8 or a reduction product of the formula 12 or 16.

According to this process, the desired optically active alcohol compounds 27 and 28 can be prepared by reacting a vinyl ester derivative of the formula 25 to a racemic alcohol derivative of the formula 24 in the presence of a lipase, separating the obtained optically active ester derivative 26 and the optically active alcohol derivative, and then hydrolyzing the ester group with respect to the optically active ester derivative 26.

R^t of the vinyl ester derivative of the formula 25 is preferably a lower alkyl group such as a methyl group or an ethyl group; an aryl group such as a phenyl group or a naphthyl group; or an aralkyl group such as a benzyl group or a 2-phenylethyl group. Particularly preferred is a methyl group, i.e. a case wherein the compound of the formula 25 is vinyl acetate or isopropenyl acetate.

The above optical resolution reaction by lipase can be conducted usually in an inert solvent such as methylene chloride, chloroform, ethyl ether, tetrahydrofuran, benzene, toluene, hexane, heptane or acetonitrile, or by using the starting material vinyl ester derivative of the formula 25 itself as the solvent.

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The vinyl ester derivative 25 is used usually in an amount of 1 mol or in a large excess molar amount, preferably from 1 to 100 mols, per mol of the starting material compound 24, and the amount of the lipase as the catalyst is from 0.01 to 100%, preferably from 0.1 to 20%, by weight, relative to the compound 24.

The type of the lipase is preferably a lipase derivative from *Pseudomonas* sp. such as Toyothium LIPTM (manufactured by Toyobo).

Further, the above enzymatic reaction tends to be accelerated, when the reaction is carried out in the presence of a base. As a base to be used for this purpose, an organic base such as triethylamine or diisopropylethylamine, is preferred.

The base is used usually in an amount of 0.01 mol or slightly excess molar amount, preferably from 0.1 to 1.5 mols, relative to the starting material compound 24.

The reaction temperature is usually from 0°C to 50°C, preferably from room temperature to 40°C. The reaction time is usually from 30 minutes to 7 days, preferably from 1 hour to 48 hours.

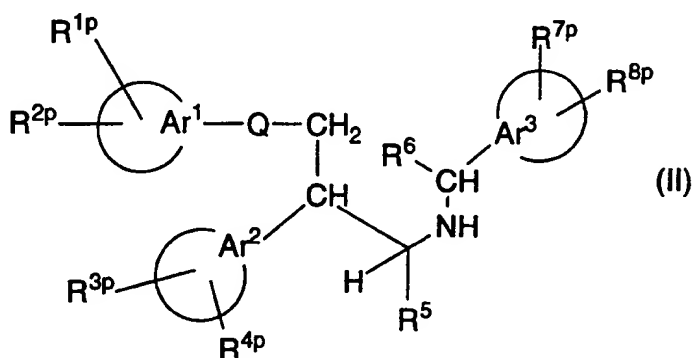
The hydrolytic reaction of the ester of the formula 26 can be conducted by a common method well known in the organic synthetic chemistry under an acidic or basic condition.

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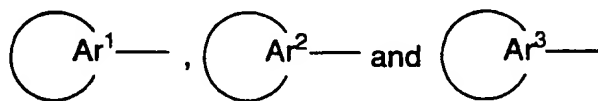
The compound of the formula (hh) of the present invention can be prepared, for example, by the following process 1, 2, 3, 4, 5, 6 or 7.

5 Process 1

The compound of the formula (hh) can be prepared by reacting a compound of the formula (II):



10

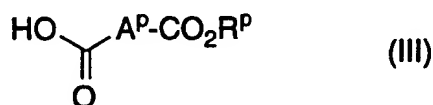


wherein each of Ar^1 , Ar^2 and Ar^3 which are the same or different, is an aryl group or a heteroaromatic ring group; Q is a group of the formula $-(\text{CH}_2)_m-$ (wherein m is an integer of from 1 to 6) or $-(\text{CH}_2)_n-\text{W}-(\text{CH}_2)_p-$ (wherein W is an oxygen atom, a sulfur atom, a vinylene group or an ethynylene group; and each of n and p which are the same or different, is an integer of from 0 to 3); R^{1p} is a hydrogen atom, a halogen atom, a hydroxyl group which may be protected, a lower alkyl group, a lower alkoxy group, or an aryl or heteroaromatic ring group which may have substituent(s) selected from the group consisting of a halogen atom, a lower alkyl group and a lower alkoxy group; each of R^{2p} , R^{7p} and R^{8p} which are the same or different, is a hydrogen atom, a halogen atom, a hydroxyl group which may be protected, a lower alkyl group or a lower alkoxy group; each of R^{3p} and R^{4p} which are the same or different, is a hydrogen atom, a halogen atom, a nitro group, a cyano group, a lower alkoxycarbonyl

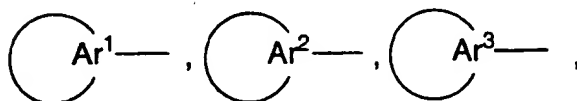
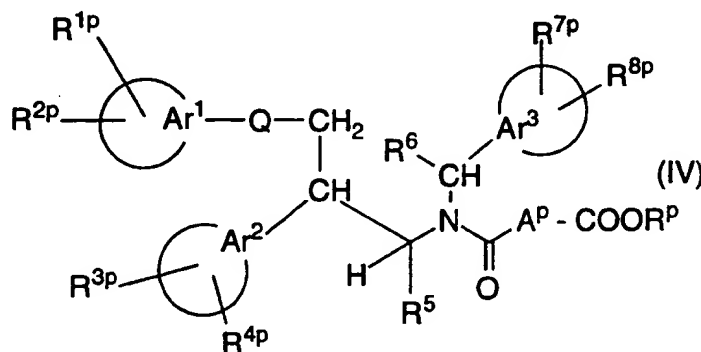
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- group, a carbamoyl group, a lower alkylcarbamoyl group, a lower alkyl group, a lower fluoroalkyl group, a lower alkoxy group or a hydroxyl, amino, carboxyl or lower hydroxyalkyl group which may be protected; R^5 is a lower alkyl group; and R^6 is a hydrogen atom or a lower alkyl group, with a carboxylic acid of the formula (III) or its reactive derivative:



- 10 wherein AP is a C₂-8 saturated or unsaturated aliphatic hydrocarbon group which may have substituent(s) selected from the group consisting of a lower alkyl group, a lower alkoxy group, an aryl group, an aralkyl group, and hydroxyl, lower hydroxyalkyl, carboxyl and lower carboxyalkyl groups which may be protected; and R^p is a hydrogen atom or a carboxyl-protecting group, to obtain a compound of the formula (IV):



- 20 wherein Ar^1 , Ar^2 , Ar^3 , AP, Q, R^{1p} , R^{2p} , R^{3p} , R^{4p} , R^5 , R^6 , R^{7p} , R^{8p} and R^p are as defined above, and, if necessary, removing any protecting group.

As the reactive derivative of the carboxylic acid of the formula (III), an acid halide, a mixed acid anhydride, an active ester or an active amide may, for example, be used.

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When the carboxylic acid of the formula (III) is used, it is preferred to conduct the reaction in the presence of a condensing agent such as N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide or 2-chloro-1,3-dimethylimidazolyl chloride.

The reaction of the compound of the formula (II) with the carboxylic acid of the formula (III) or its reactive derivative, is conducted usually by using 1 mol or an excess molar amount, preferably from 1 to 5 mols, of the carboxylic acid of the formula (III) or its reactive derivative, per mol of the compound of the formula (II).

The reaction is conducted usually in an inert solvent. The inert solvent may, for example, be a halogenated hydrocarbon such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane or trichloroethylene; an ether such as ethyl ether, tetrahydrofuran or dioxane; an aromatic hydrocarbon such as benzene, toluene, chlorobenzene or xylene; an aprotic polar solvent such as dimethylformamide, acetonitrile, acetone, ethyl acetate or hexamethylphosphoric triamide, or a mixture of such solvents.

The reaction temperature is usually from -70°C to the boiling point of the solvent used for the reaction, preferably from -20°C to 100°C.

The reaction time is usually from 5 minutes to 7 days, preferably from 10 minutes to 24 hours.

The above reaction can be conducted in the presence of a base to facilitate the reaction. As such a base, it is preferred to conduct the reaction in the presence of an inorganic base such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate or sodium hydrogen carbonate, or an organic base such as triethylamine, N-ethyldiisopropylamine, pyridine, 4-dimethylaminopyridine or N,N-dimethylaniline.

Such a base is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the reactive derivative of the carboxylic acid of the formula (III).

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The acid halide of the compound of the formula (III) can be obtained by reacting the carboxylic acid of the formula (III) with a halogenating agent in accordance with a conventional method. As the halogenating agent, thionyl chloride, phosphorus trichloride, 5 phosphorus pentachloride, phosphorus oxychloride, phosphorus tribromide, oxalyl chloride or phosgene may, for example, be used.

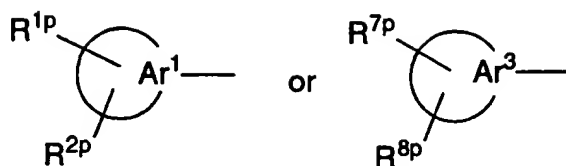
The mixed acid anhydride of the compound of the formula (III) can be obtained by reacting the carboxylic acid of the formula (III) with an alkyl chlorocarbonate such as ethyl 10 chlorocarbonate or with an aliphatic carboxylic acid chloride such as acetyl chloride, in accordance with a conventional method. Further, an intramolecular acid anhydride may be formed between carboxyl groups at both terminals, or when in the formula (III), a carboxyl group is present on the saturated or unsaturated aliphatic hydrocarbon group for 15 AP, an intramolecular acid anhydride may be formed between such a carboxyl group and a carboxyl group to be involved in the reaction, to constitute a reactive derivative of the carboxylic acid.

The active ester of the compound of the formula (III) can be prepared by reacting the carboxylic acid of the formula (III) with an 20 N-hydroxy compound such as N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxybenzotriazole, or a phenol compound such as a 4-nitrophenol, 2,4-dinitrophenol, 2,4,5-trichlorophenol or pentachlorophenol, in the presence of a condensing agent such as N,N'-dicyclohexylcarbodiimide or 1-ethyl-3-(3- 25 dimethylaminopropyl)carbodiimide in accordance with a conventional method.

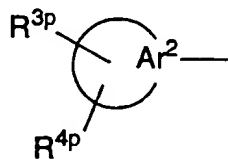
The active amide of the compound of the formula (III) can be prepared by reacting the carboxylic acid of the formula (III) with e.g. 1,1'-carbonyldiimidazole or 1,1'-carbonylbis(2-methylimidazole) in 30 accordance with a conventional method.

When a hydroxyl group is present on the group of the formula

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- when a hydroxyl group, a lower hydroxyalkyl group, a carboxyl group or a lower carboxyalkyl group is present on the saturated or unsaturated aliphatic hydrocarbon group represented by AP, and when a hydroxyl group, an amino group, a carboxyl group or a lower hydroxyalkyl group is present on the group of the formula



- it is preferred to conduct the reaction after protecting such a hydroxyl group, a lower hydroxyalkyl group, an amino group, a carboxyl group or a lower carboxyalkyl group appropriately by a hydroxyl-protecting group, an amino-protecting group or a carboxyl-protecting group and removing the protecting group after the reaction.

- The hydroxyl-protecting group may, for example, be a lower alkylsilyl group such as a trimethylsilyl group or a tert-butyldimethylsilyl group; a lower alkoxymethyl group such as a methoxymethyl group or a 2-methoxyethoxymethyl group; a tetrahydropyranyl group; an aralkyl group such as a benzyl group, a p-methoxybenzyl group, a p-nitrobenzyl group or a trityl group; or an acyl group such as a formyl group or an acetyl group. Particularly preferred is a methoxymethyl group, a tetrahydropyranyl group, a trityl group, a tert-butyldimethylsilyl group or an acetyl group.

- The amino-protecting group may, for example, be an aralkylidene group such as a benzylidene group, a p-chlorobenzylidene group or a p-nitrobenzylidene group; an aralkyl group such as a benzyl group, a p-methoxybenzyl group, a p-nitrobenzyl group, a benzhydryl group or a trityl group; a lower alkanoyl group such as a formyl group, an acetyl group, a propionyl group, a butyryl group or a pivaloyl

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group; a lower haloalkanoyl group such as a trifluoroacetyl group; a lower alkoxy carbonyl group such as a methoxy carbonyl group, an ethoxy carbonyl group, a propoxy carbonyl group or a tert-butoxy carbonyl group; a lower haloalkoxy carbonyl group such as a 2,2,2-trichloroethoxy carbonyl group; an alkenyloxy carbonyl group such as a 2-propenyloxy carbonyl group; an aralkyloxy carbonyl group such as a benzyloxy carbonyl group or a p-nitrobenzyloxy carbonyl group; or a lower alkylsilyl group such as a trimethylsilyl group or a tert-butyldimethylsilyl group. Particularly preferred is an acetyl group, a trifluoroacetyl group, a tertbutoxy carbonyl group or a benzyloxy carbonyl group.

The carboxyl-protecting group may, for example, be a lower alkyl group such as a methyl group, an ethyl group, a propyl group, an isopropyl group or a tert-butyl group; a lower haloalkyl group such as a 2,2,2-trichloroethyl group; a lower alkenyl group such as 2-propenyl group; or an aralkyl group such as a benzyl group, a p-methoxybenzyl group, a p-nitrobenzyl group, a benzhydryl group or trityl group. Particularly preferred is a methyl group, an ethyl group, a tert-butyl group, a 2-propenyl group, a benzyl group, a p-methoxybenzyl group or a benzhydryl group.

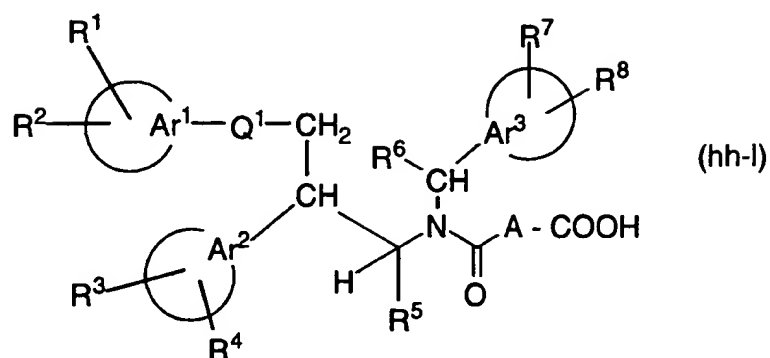
After completion of the reaction, conventional treatment is conducted to obtain a crude product of the compound of the formula (IV). The compound of the formula (IV) may or may not be purified in accordance with a conventional method, and if necessary, reactions for removing protecting groups such as a hydroxyl group, an amino group and a carboxyl group, are appropriately conducted to obtain a compound of the formula (hh).

Removal of protecting groups may vary depending upon their types, but can be conducted in accordance with the methods disclosed in a literature (Protective Groups in Organic Synthesis, T.W. Greene, John Wiley & Sons (1981)) or methods similar thereto, for example by solvolysis employing an acid or a base, by chemical reduction employing a metal hydride complex or by catalytic reduction employing a palladium-carbon catalyst or Raney nickel.

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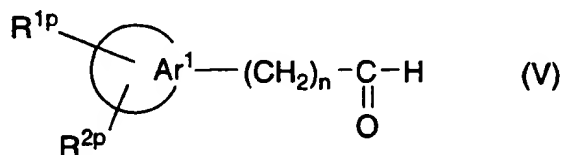
Process 2

A compound of the formula (hh-1):



- 5 wherein Q^1 is $-(CH_2)_n-CH=CH-(CH_2)_p-$ (wherein n and p are as defined

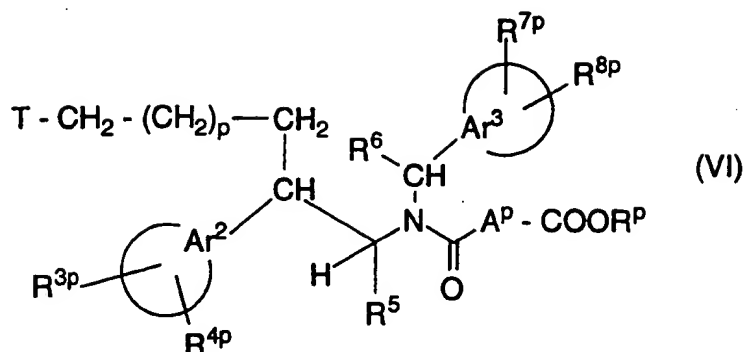
above); and Ar^1 , Ar^2 , Ar^3 , A , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are as defined above, can be prepared by reacting a compound of the formula (V):



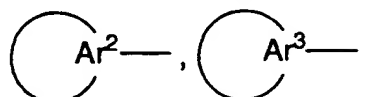
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wherein Ar^1 , R^{1p} , R^{2p} and n are as defined above, with a compound of the formula (VI):

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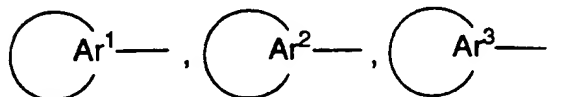
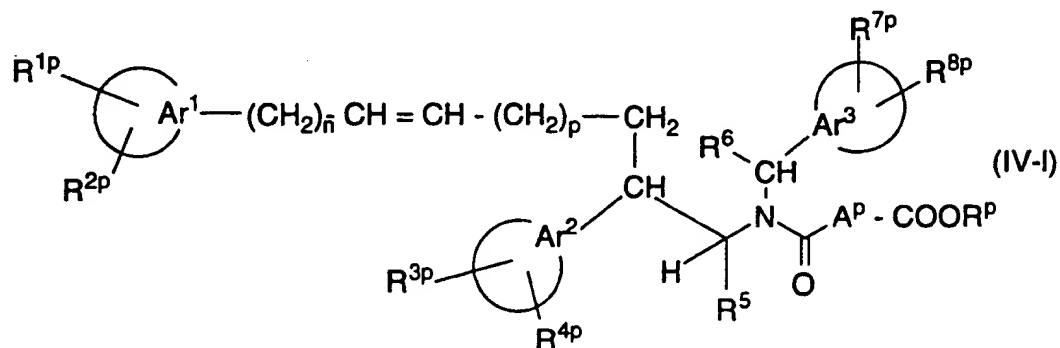
wherein T is a triphenylphosphonio group, a dimethoxyphosphoryl



group or a diethoxyphosphoryl group; and

AP, p, R^{3p}, R^{4p}, R⁵, R⁶, R^{7p}, R^{8p} and R^p are as defined above, to

5 obtain a compound of the formula (IV-1):



wherein

AP, n, p, R^{1p}, R^{2p},

R^{3p}, R^{4p}, R⁵, R⁶, R^{7p}, R^{8p} and R^p are as defined above, and, if

10 necessary, removing any protecting group.

Process 2 is a process for preparing a compound of the formula (hh) wherein Q is $-(CH_2)_n-CH=CH-(CH_2)_p-$ (wherein n and p are as defined above) i.e. a compound of the formula (hh-1).

The reaction of the compound of the formula (V) with a
15 compound of the formula (VI) is carried out usually by employing

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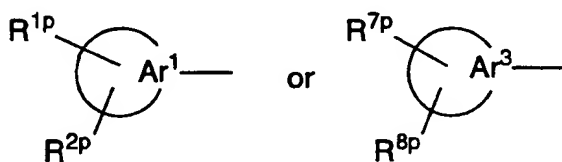
equimolar amounts of the two reactants or using a slightly excess amount of one of them.

The reaction is carried out usually in an inert solvent. Such an inert solvent may, for example, be an ether such as ethyl ether, tetrahydrofuran or dioxane; an aromatic hydrocarbon such as benzene, toluene, chlorobenzene or xylene; an aprotic polar solvent such as dimethylformamide, acetonitrile, acetone, ethyl acetate or hexamethylphosphoric triamide; or a mixture of such solvents.

The reaction temperature is usually from -100°C to the boiling point of the solvent used for the reaction, preferably from -70°C to 50°C .

The reaction time is usually from 5 minutes to 7 days, preferably from 10 minutes to 24 hours. Further, the above reaction can be conducted in the presence of a base to facilitate the reaction. Especially when T in the formula (VI) is a triphenylphosphonio group, the reaction is preferably conducted in the presence of a base such as sodium hydride, n-butyl lithium, sodium methoxide, potassium tert-butoxide, sodium hydroxide or potassium hydroxide.

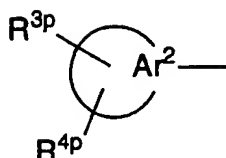
Such a base is used in an amount of one mol or an excess molar amount, preferably from 1 to 5 mols per mol of the compound wherein T is a triphenylphosphonio group. When a hydroxyl group is present on the group of the formula



when a hydroxyl group, a lower hydroxyalkyl group, a carboxyl group or a lower carboxyalkyl group is present on the saturated or unsaturated aliphatic hydrocarbon group represented by AP, and when a hydroxyl group, an amino group, a carboxyl group or a lower hydroxyalkyl group is present on the group of the formula

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it is preferred to carry out the reaction after protecting such a hydroxyl group, a lower hydroxyalkyl group, an amino group, a carboxyl group or a lower carboxyalkyl group appropriately by a hydroxyl-protecting group, an amino-protecting group or a carboxyl-protecting group, and removing any protecting group after the reaction.

The hydroxyl-protecting group, the amino-protecting group and the carboxyl-protecting group may be the protecting groups mentioned above with respect to process 1.

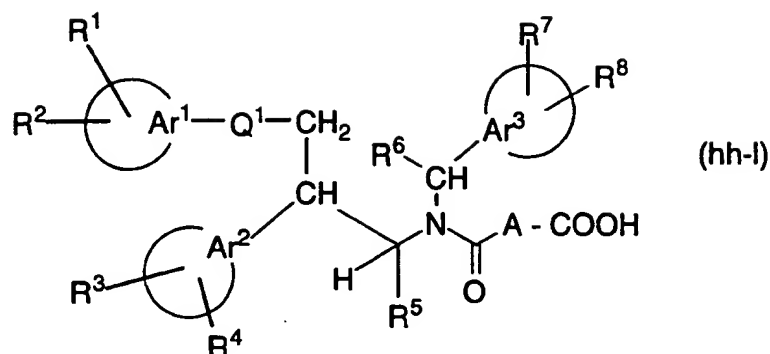
After completion of the reaction, a conventional treatment may be carried out to obtain a crude product of the compound of the formula (IV-1). The compound of the formula (IV-1) thus obtained may or may not be purified by a conventional method, and if necessary, reactions for removing hydroxyl-, amino- and carboxyl-protecting groups may be carried out in a proper combination to obtain a compound of the formula (hh-1).

The method for removing a protecting group varies depending upon the type of the protecting group and the stability of the desired compound (hh-1). However, removal of protecting groups can be suitably conducted in accordance with the methods disclosed in the above-mentioned literature or methods similar thereto.

Process 3

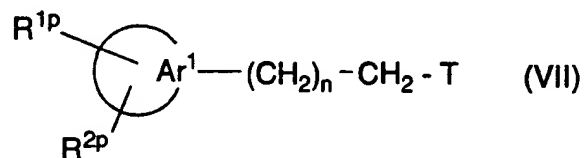
A compound of the formula (hh-1):

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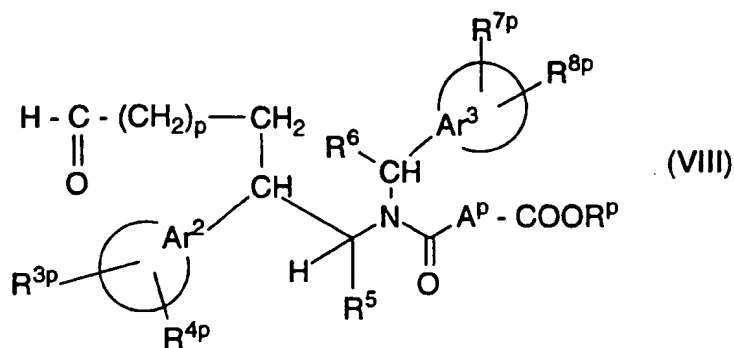


wherein Ar^1 —, Ar^2 —, Ar^3 —, A, Q¹, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as defined above, can be obtained by reacting a compound of the formula (VII):

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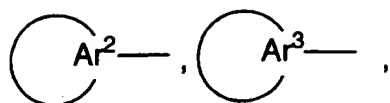


wherein Ar^1 —, T, n, R^{1p} and R^{2p} are as defined above, with a compound of the formula (VIII):

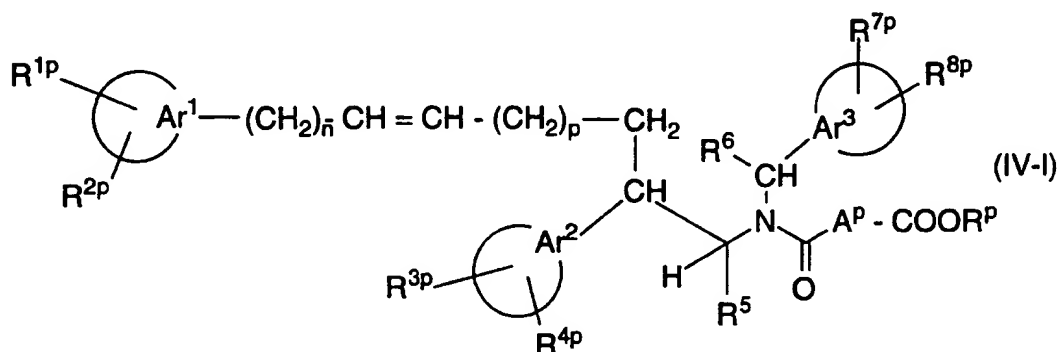


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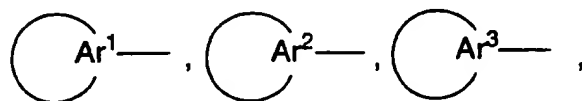
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wherein AP, p, R^{3p}, R^{4p}, R⁵, R⁶, R^{7p}, R^{8p} and RP are as defined above, to obtain a compound of the formula (IV-1):



5



wherein AP, n, p, R^{1p}, R^{2p}, R^{3p}, R^{4p}, R⁵, R⁶, R^{7p}, R^{8p} and RP are as defined above, and, if necessary, removing any protecting group.

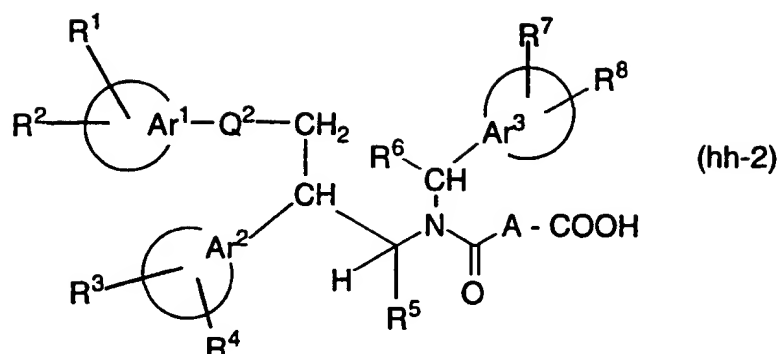
Like process 2, process 3 is a process for producing a compound of the formula (hh) wherein Q is $-(\text{CH}_2)_n\text{---CH=CH---}(\text{CH}_2)_p\text{---}$ (wherein n and p are as defined above) i.e. a compound of the formula (hh-1).

Process 3 is equal to the reaction of process 2 wherein starting material compounds (V) and (VI) are replaced by the compounds (VIII) and (VII), respectively. Accordingly, the manner and conditions of the reaction may be all in accordance with process 2.

Process 4

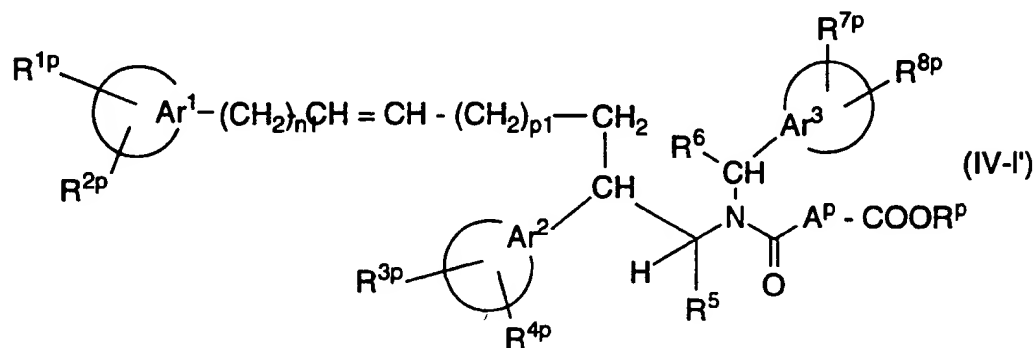
A compound of the formula (hh-2):

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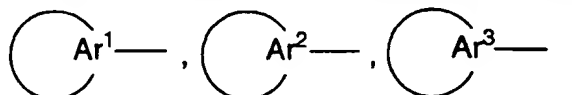


wherein Q^2 is $-(CH_2)_m-$ (wherein m is as defined above);

and Ar^1 , Ar^2 , Ar^3 , A , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are as defined above, can be obtained by reducing a
 5 compound of the formula (IV-1'):



wherein each of n_1 and p_1 which are the same or different, is an integer



of from 0 to 3; and

- 10 AP , R^{1p} , R^{2p} , R^{3p} , R^{4p} , R^5 , R^6 , R^{7p} , R^{8p} and RP are as defined above (provided that the sum of n_1 and p_1 does not exceed 4), and, if necessary, removing any protecting group.

- Process 4 is a process for producing a compound of the formula (hh) wherein Q is $-(CH_2)_m-$ (wherein m is as defined above)
 15 i.e. a compound of the formula (hh-2).

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The reaction of reducing the compound of the formula (IV-1') is usually preferably conducted by catalytic reduction employing a palladium-carbon catalyst, a Raney nickel catalyst or a platinum catalyst in an inert solvent.

5 The inert solvent may, for example, be an alcohol such as methanol, ethanol or propanol, or acetic acid.

The reaction temperature is usually from -20°C to 100°C, preferably from 0°C to room temperature.

10 The reaction time is usually from 5 minutes to 7 days, preferably from 10 minutes to 24 hours.

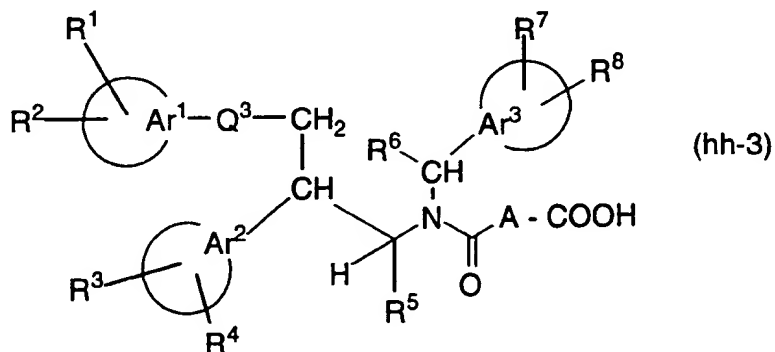
The hydrogen pressure in the catalytic reduction reaction is usually preferably from atmospheric pressure to 5 atm, and the amount of the catalyst is usually from 0.01 to 1 mol, preferably from 0.05 to 0.2 mol, per mol of the starting material compound (IV-1').

15 After completion of the reaction, the product is subjected to a usual treatment after removing any protecting group if such a protecting group is present or directly if no such protecting group is present, to obtain a compound of the formula (hh-2).

20 Removal of the protecting group and the post treatment may be conducted by the methods described with respect to the above process 1.

Process 5

25 A compound of the formula (hh-3);

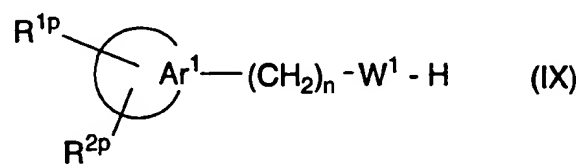


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wherein Q^3 is $-(CH_2)_n-W^1-(CH_2)_p-$ (wherein n , p and W^1 are as defined

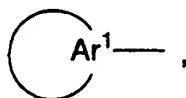
above); and \bigcirc_{Ar^1} , \bigcirc_{Ar^2} , \bigcirc_{Ar^3} , A , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are as defined above, can be prepared by reacting a compound of the formula (IX):

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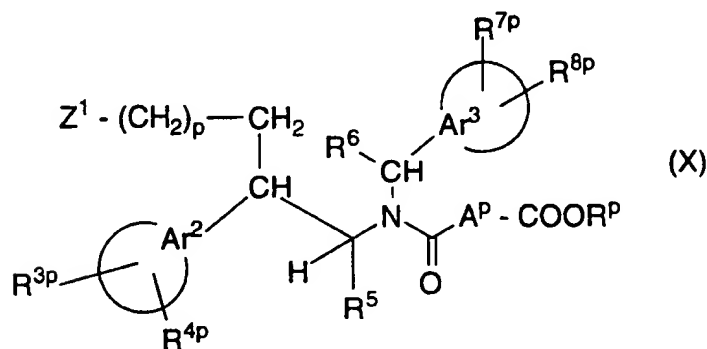


wherein W^1 is an oxygen atom or a sulfur atom; and

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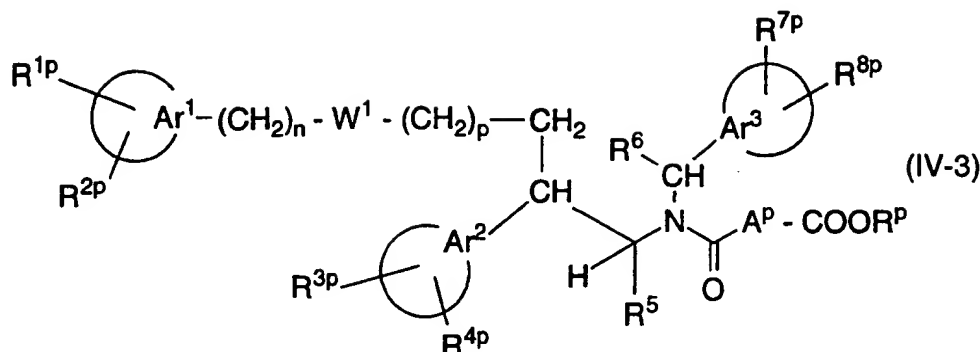
n , R^{1p} and R^{2p} are as defined above, with a compound of the formula (X):



15

wherein Z^1 is a leaving group, and \bigcirc_{Ar^2} , \bigcirc_{Ar^3} , AP , p , R^{3p} , R^{4p} , R^5 , R^6 , R^{7p} , R^{8p} and R^p are as defined above, to obtain a compound of the formula (IV-3);

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wherein Ar^1 —, Ar^2 —, Ar^3 —, AP , n , p , W^1 , R^{1p} , R^{2p} , R^{3p} , R^{4p} , R^5 , R^6 , R^{7p} , R^{8p} and RP are as defined above, and, if necessary, removing any protecting group.

- 5 Process 5 is a process for preparing a compound of the formula (hh) wherein Q is $-(\text{CH}_2)_n-\text{W}^1-(\text{CH}_2)_p-$ (wherein n , p and W^1 are as defined above) i.e. a compound of the formula (hh-3).

10 The reaction of the compound of the formula (IX) with a compound of the formula (X) is carried out usually by using 1 mol or an excess molar amount, preferably from 1 to 3 mols, of the compound of the formula (IX), per mol of the compound of the formula (X).

15 The reaction is conducted usually in an inert solvent. The inert solvent may, for example, be a halogenated hydrocarbon such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane or trichloroethylene; an ether such as ethyl ether, tetrahydrofuran or dioxane; an aromatic hydrocarbon such as benzene, toluene, chlorobenzene or xylene; an aprotic polar solvent such as dimethylformamide, acetonitrile, acetone, ethyl acetate or hexamethylphosphoric triamide, or a mixture of such solvents.

20 The reaction temperature is usually from -70°C to the boiling point of the solvent used for the reaction, preferably from -20°C to 100°C .

 The reaction time is usually from 5 minutes to 7 days, preferably from 10 minutes to 24 hours.

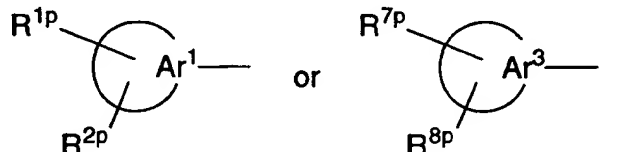
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The above reaction is preferably conducted in the presence of a base to facilitate the reaction. Such a base may, for example, be an inorganic base such as sodium hydride, n-butyl lithium, sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate or sodium hydrogencarbonate, or an organic base such as triethylamine, N-ethyl-diisopropylamine, pyridine, 4-dimethylaminopyridine or N,N-dimethylaniline.

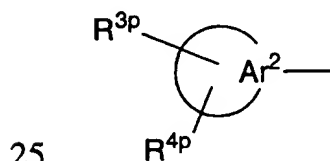
The base is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the compound of the formula (IX).

The leaving group represented by Z^1 may, for example, be a halogen atom such as a chlorine atom, a bromine atom or an iodine atom, or an organic sulfonyloxy group such as a methanesulfonyloxy group, a p-toluenesulfonyloxy group or a benzenesulfonyloxy group.

When a hydroxyl group is present on the group of the formula



when a hydroxyl group, a lower hydroxyalkyl group, a carboxyl group or a lower carboxyalkyl group is present on the saturated or unsaturated aliphatic hydrocarbon group represented by AP, and when a hydroxyl group, an amino group, a carboxyl group or a lower hydroxyalkyl group is present on the group of the formula



it is preferred to conduct the reaction after protecting such a hydroxyl group, a lower hydroxyalkyl group, an amino group, a carboxyl group or a lower alkoxyalkyl group appropriately by a hydroxyl-protecting group, an amino-protecting group or a carboxyl-protecting group and

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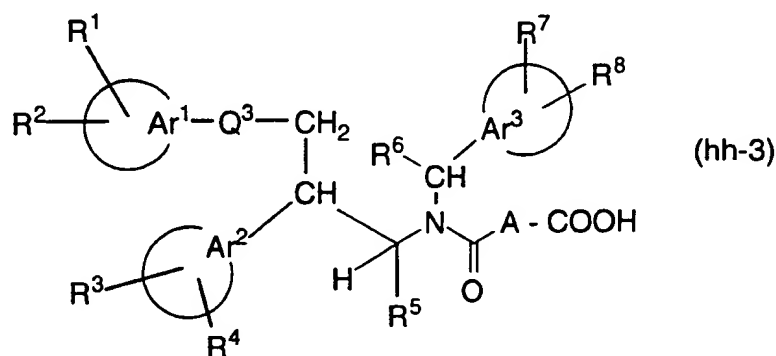
removing any protecting group after the reaction.

The hydroxyl-protecting group, the amino-protecting group and the carboxyl-protecting group may be the protecting groups mentioned above with respect to process 1.

- 5 After completion of the reaction, a usual treatment is carried out to obtain a crude product of the compound of the formula (IV-3). The compound of the formula (IV-3) thus obtained may or may not be purified by a conventional method, and reactions for removing the hydroxyl-, amino- and carboxyl-protecting groups may be carried out in a proper combination, to obtain a compound of the formula (hh-3). The method for removing a protecting group varies depending upon the type of the protecting group and the stability of the desired compound (hh-3). However, removal of protecting groups can be appropriately conducted in accordance with the methods disclosed in the above-mentioned literature or methods similar thereto.

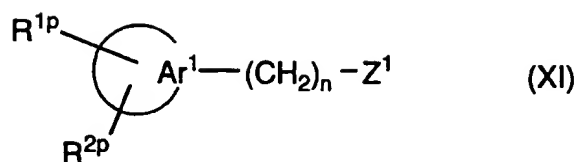
Process 6

A compound of the formula (hh-3):

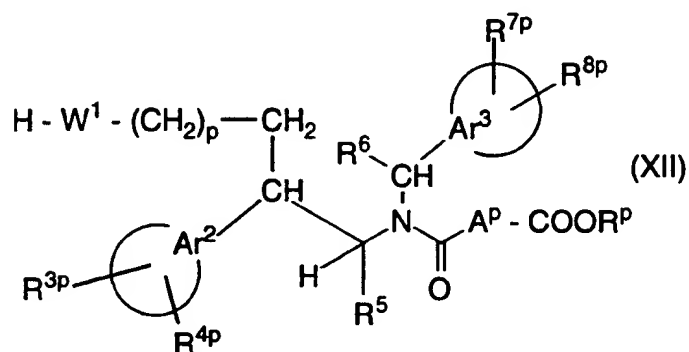


- 20 wherein $\bigcirc\text{Ar}^1$ —, $\bigcirc\text{Ar}^2$ —, $\bigcirc\text{Ar}^3$ —, A, Q³, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as defined above, can be prepared by reacting a compound of the formula (XI):

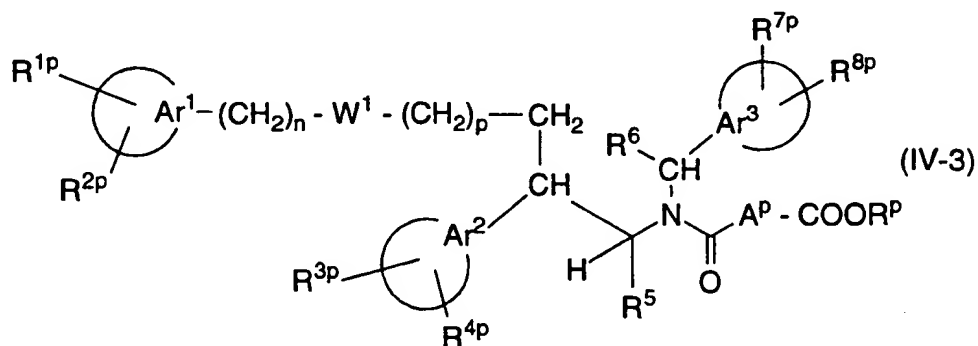
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wherein Ar^1 —, n , Z^1 , R^{1p} and R^{2p} are as defined above, with a
 5 compound of the formula (XII):



wherein Ar^2 —, Ar^3 —, A^p , p , W^1 , R^{3p} , R^{4p} , R^5 , R^6 ,
 R^{7p} , R^{8p} and R^p are as defined above, to obtain a compound of the
 formula (IV-3):



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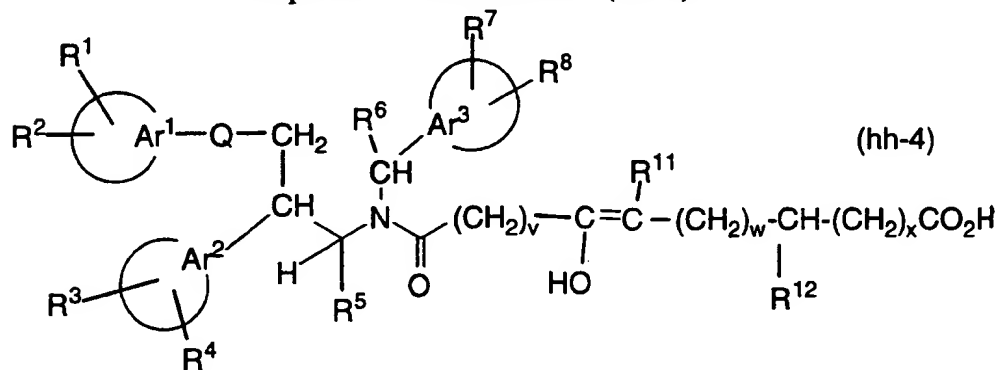
wherein $\bigcirc\text{Ar}^1\text{---}$, $\bigcirc\text{Ar}^2\text{---}$, $\bigcirc\text{Ar}^3\text{---}$, AP, n, p, W¹, R^{1p}, R^{2p}, R^{3p}, R^{4p}, R⁵, R⁶, R^{7p}, R^{8p} and RP are as defined above, and, if necessary, removing any protecting group.

Like the above process 5, process 6 is a process for
 5 preparing a compound of the formula (hh) wherein Q is $-(\text{CH}_2)_n\text{---W}^1\text{---}(\text{CH}_2)_p\text{---}$ (wherein n, p and W¹ are as defined above) i.e. a compound of the formula (hh-3).

This process can be conducted usually in an inert solvent,
 preferably in the presence of a base, by using 1 mol or an excess molar
 10 amount, preferably from 1 to 3 mols, of the compound of the formula (XI), per mol of the compound of the formula (XII). The types of the inert solvent and the base as well as the reaction conditions may be the same as described above with respect to process 5. Accordingly, the reaction and the post-treatment after the reaction may preferably be
 15 carried out all in accordance with process 5.

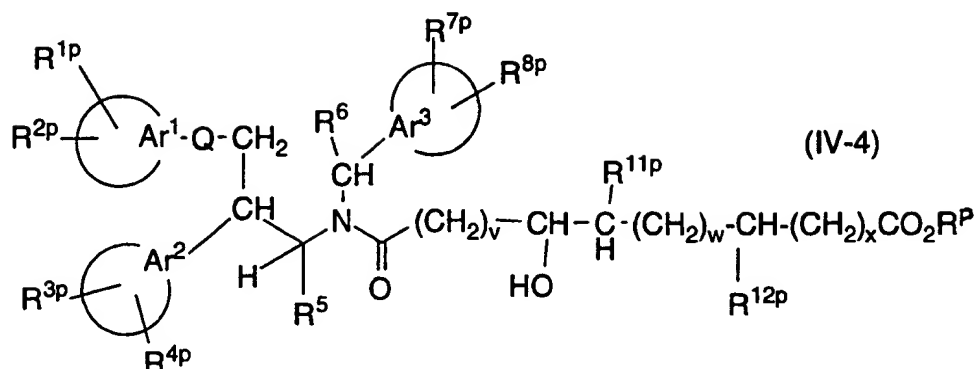
Process 7

A compound of the formula (hh-4):

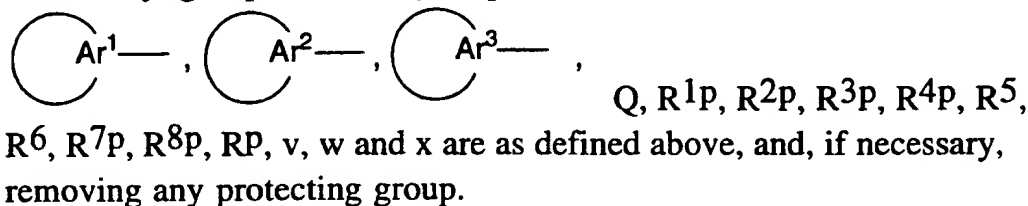


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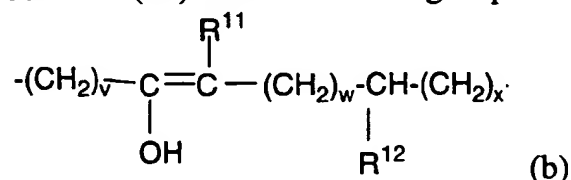
wherein $\bigcirc\text{Ar}^1\text{---}$, $\bigcirc\text{Ar}^2\text{---}$, $\bigcirc\text{Ar}^3\text{---}$, Q, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R¹¹, R¹², v, w and x are as defined above, can be prepared by oxidizing a compound of the formula (IV-4):



- wherein R^{11p} is a hydrogen atom or a lower hydroxyalkyl or carboxyl
5 group which may be protected, R^{12p} is a hydrogen atom or a hydroxyl
or carboxyl group which may be protected; and



- 10 Process 7 is a process for preparing a compound of the formula (hh) wherein A is a group of the formula (b):



- wherein R¹¹, R¹², v, w and x are as defined above, i.e. a compound of
15 the formula (hh-4).

- The reaction of oxidizing the compound of the formula (IV-4) is usually preferably carried out in an inert solvent by using so-called Dess-Martin oxidation employing 12-I-5 triacetoxyperiodinane; so-called Swern oxidation employing oxalyl chloride and dimethyl sulfoxide; a sulfur trioxide-pyridine complex; pyridinium chlorochromate; active manganese dioxide; or tetra-n-propylammonium perruthenate.

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The inert solvent may, for example, be a halogenated hydrocarbon such as methylene chloride, chloroform or dichloroethane; an ether such as ethyl ether, tetrahydrofuran or dioxane; an aprotic polar solvent such as acetonitrile, acetone, ethyl acetate or dimethyl sulfoxide; or a mixture of such solvents.

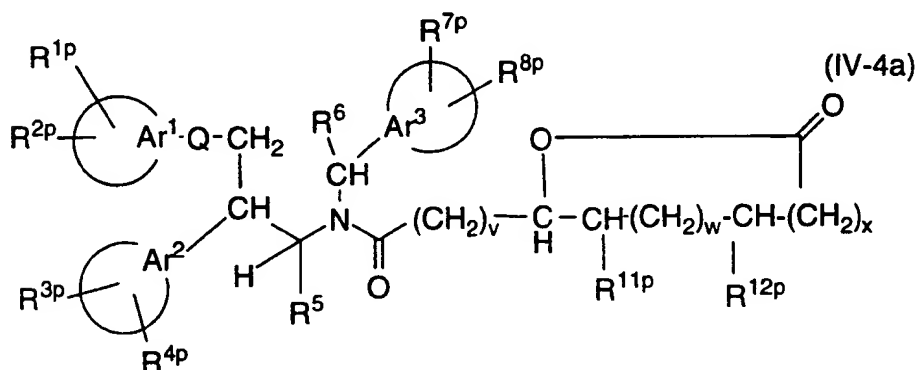
The reaction temperature varies depending upon the type of the oxidizing agent, etc. However, it is usually from -100°C to the boiling point of the solvent used for the reaction, preferably from -70°C to 100°C .

The reaction time is usually from 5 minutes to 7 days, preferably from 10 minutes to 24 hours.

After completion of the reaction, the product is subjected to usual treatment after removing a protecting group when such a protecting group is present, or directly when no such protecting group is present, to obtain the compound of the formula (hh-4).

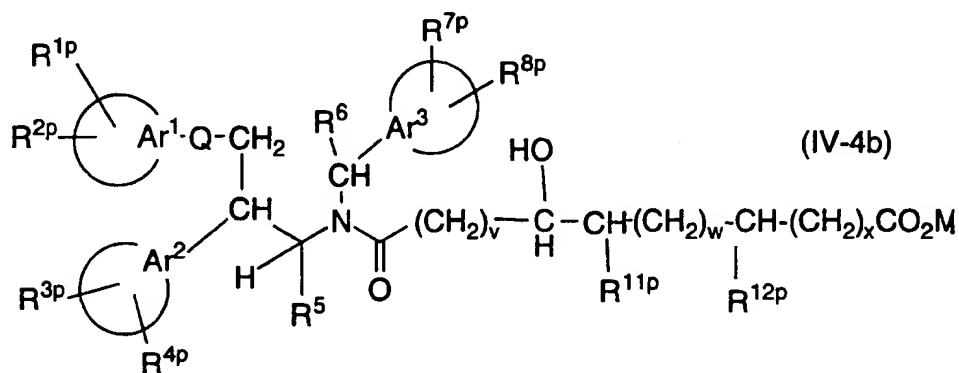
The removal of the protecting group and the post-treatment may be conducted in the same manner as described above with respect to process 1.

Further, a compound corresponding to the compound of the formula (IV-4) to be used as the starting material in the above process 7, can be prepared, for example, by hydrolyzing a compound of the formula (IV-4a):



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wherein $\bigcirc\text{Ar}^1\text{---}$, $\bigcirc\text{Ar}^2\text{---}$, $\bigcirc\text{Ar}^3\text{---}$, Q, R^{1p}, R^{2p}, R^{3p}, R^{4p}, R⁵, R⁶, R^{7p}, R^{8p}, R^{11p}, R^{12p}, v, w and x are as defined above, in the presence of a base, to obtain a compound of the formula (IV-4b):



wherein M is a hydrogen atom or an alkali metal atom; and

10 $\bigcirc\text{Ar}^1\text{---}$, $\bigcirc\text{Ar}^2\text{---}$, $\bigcirc\text{Ar}^3\text{---}$, Q, R^{1p}, R^{2p}, R^{3p}, R^{4p}, R⁵, R⁶, R^{7p}, R^{8p}, R^{11p}, R^{12p}, v, w and x are as defined, then reacting thereto a diazo compound of the formula



15 wherein RPP is a lower alkyl group, a lower alkenyl group, an aralkyl group or a lower alkoxy carbonylalkyl group, or an alkylating agent of the formula RPP-Z wherein RPP and Z are as defined above.

20 Isolation and purification of the compound of the formula (hh), (hh-I), (hh-2), (hh-3) or (hh-4), obtained by the above process can be conducted by a single use or a proper combination of conventional separating means such as column chromatography employing silica gel, adsorbent resin, etc., liquid chromatography, solvent extraction and recrystallization-reprecipitation.

The compound of the formula (hh), (hh-I), (hh-2), (hh-3) or (hh-4) can be converted to a pharmaceutically acceptable salt or ester

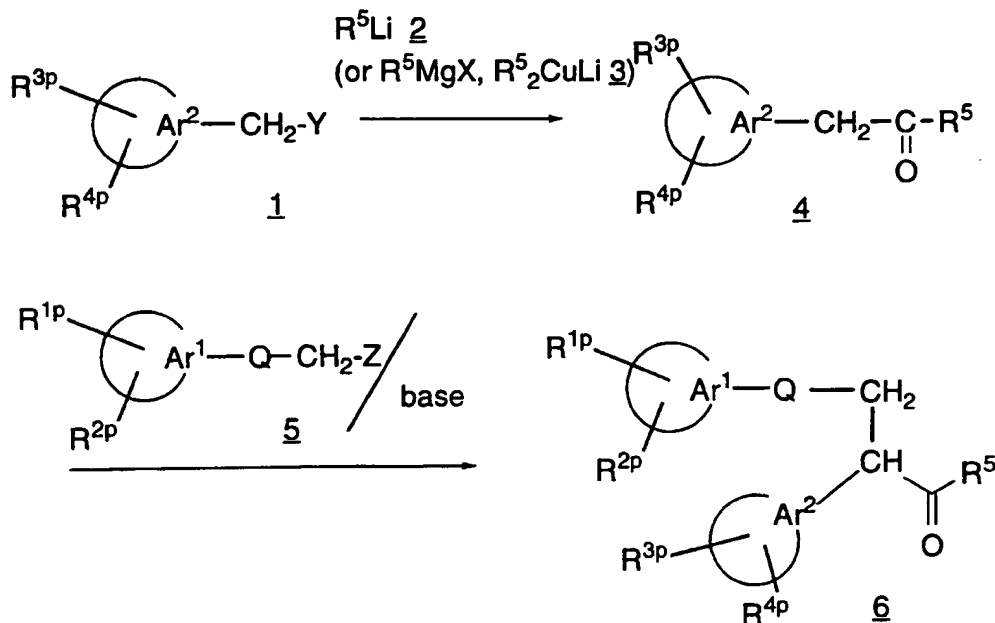
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by a conventional method. Reversely, the conversion from the salt or ester to a free carboxylic acid can also be conducted by a conventional method.

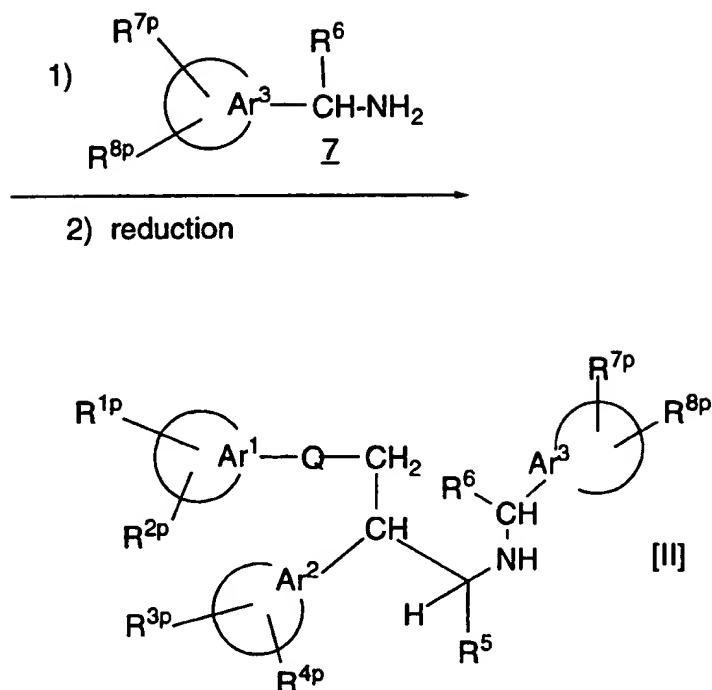
Further, compounds of the present invention can all be prepared by a process similar to the above processes by using the starting materials corresponding to the desired compounds.

The compounds of the formulas (II), (III), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) may be commercially available or can be prepared in accordance with the methods disclosed in literatures (J. Med. Chem., 10, 717 (1967); *ibid.*, 725; J. Chem. Soc. Perkin 1, 1636 (1978); Chem. Lett., 191 (1980); *ibid.*, 375 (1984); J. Chem. Soc. Chem. Commun., 579 (1984); J. Am. Chem. Soc., 104, 5716 (1982)) or methods similar thereto, or in accordance with the following processes or the methods disclosed in Examples.

Process A



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- In the above formulas, Q, R^{1p}, R^{2p}, R^{3p}, R^{4p}, R⁵, R⁶, R^{7p} and R^{8p} are as defined above; X is a halogen atom; Y is a cyano group, a carboxyl group, a lower alkoxy carbonyl group, a chloroformyl group or an N-methoxy-N-methylcarbamoyl group; Z is a leaving group selected from the group consisting of a chlorine atom, a bromine atom, an iodine atom, a trifluoroacetoxy group, a methanesulfonyloxy group, a trifluoromethanesulfonyloxy group and a p-toluenesulfonyloxy group.

By this process, the desired compound (II) can be prepared by reacting a nitrile or a carboxylic acid derivative of the formula 1 with an alkyl lithium of the formula 2 or an alkyl Grignard reagent (or an alkyl Gilman reagent) of the formula 3 to obtain a ketone compound 4, then reacting an alkylating agent of the formula 5 to the ketone compound 4 to produce a compound of the formula 6, then reacting the compound 6 with an amine compound of the formula 7, followed by reduction.

The above reaction steps will be described in detail

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referring to suitable reaction conditions, etc.

The first step of preparing the ketone compound 4 is conducted usually by reacting 1 mol or an excess molar amount, preferably from 1 to 5 mols of the alkyl lithium reagent 2 or the alkyl Grignard reagent 3 (or the alkyl Gilman reagent in the case where the substituent Y of the compound 1 is a chloroformyl group) to 1 mol of the starting material compound 1 in a solvent inert to the reaction such as tetrahydrofuran, ethyl ether or benzene, if necessary followed by hydrolysis under an acidic condition.

The reaction temperature is usually from -80°C to the boiling point of the solvent used for the reaction, preferably from -70°C to 50°C. The reaction time is usually from 5 minutes to 48 hours, preferably from 30 minutes to 24 hours.

When the substituent Y in the formula of the starting material compound 1 is a cyano group, it may be necessary to conduct a hydrolytic reaction under an acidic condition after completion of the reaction, and such a hydrolytic reaction is conducted in e.g. methanol, ethanol, tetrahydrofuran or a solvent mixture thereof with water in the presence of an acid such as hydrochloric acid, sulfuric acid or p-toluenesulfonic acid.

The reaction temperature is usually from 0°C to the boiling point of the solvent used for the reaction, and the reaction time is from 30 minutes to 24 hours.

The step of preparing the compound of the formula 6 from the ketone compound 4, can be conducted by reacting an equimolar amount or an excess molar amount, preferably from 1 to 2 mols, of the alkylating agent of the formula 5 to the ketone compound 4 in the presence of a base in an inert solvent which does not adversely affect the reaction or without using any solvent.

The inert solvent may, for example, be an ether such as ethyl ether, tetrahydrofuran or dioxane; an aromatic hydrocarbon such as benzene, toluene or xylene; an aprotic polar solvent such as dimethylformamide, dimethyl sulfoxide or hexamethylphosphoric triamide, or a mixture of such solvents.

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The base to be used for this reaction, may, for example, be an alkali metal hydride such as sodium hydride, lithium hydride or potassium hydride; a lithium amide such as lithium amide, lithium diisopropylamide or lithium bis(trimethylsilyl)amide; an alkyl lithium such as methyl lithium, butyl lithium or tert-butyl lithium; an alkali metal alkoxide such as sodium methoxide, sodium ethoxide or potassium tert-butoxide; or an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide.

The base is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the starting material alkylating agent 5.

The reaction temperature is usually from -100°C to the boiling point of the solvent used for the reaction, preferably from -80°C to 100°C. The reaction time is usually from 10 minutes to 48 hours, preferably from 30 minutes to 24 hours.

The step of preparing the desired compound (II) from the compound of the formula 6 can be conducted usually in an inert solvent such as methanol, ethanol, benzene, ethyl ether or tetrahydrofuran by reacting 1 mol or an excess molar amount, preferably from 1 to 2 mols, of the amine compound of the formula 7 to 1 mol of the compound of the formula 6 to preliminarily form an imine, which is subsequently reduced.

The reaction temperature in the process for forming the above imine is usually from 0°C to the boiling point of the solvent used for the reaction, preferably from room temperature to 100°C. The reaction time is usually from 5 minutes to 48 hours, preferably from 30 minutes to 24 hours. After the formation of the imine, the reaction solution may be used as it is to the subsequent step of the reduction reaction, or the reaction solution may be distilled or subjected to a conventional separation means to isolate the imine compound, which is then subjected to the subsequent reduction.

The reduction can be carried out by using a metal hydride complex such as sodium borohydride, sodium cyanoborohydride or

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lithium aluminum hydride, or by catalytic reduction employing a palladium-carbon catalyst or a Raney nickel catalyst.

When a metal hydride complex is used as a reducing agent, the reducing agent is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the above imine.

For the reduction, an inert solvent, for example, an alcohol such as methanol or ethanol; an ether such as dimethyl ether, ethyl ether, diisopropyl ether, dibutyl ether, dimethoxyethane, dioxane, tetrahydrofuran or diglyme; an aliphatic hydrocarbon such as pentane, hexane, heptane or cyclohexane; or an aromatic hydrocarbon such as benzene or toluene; or a mixture of such solvents, can be used appropriately as a solvent depending upon the type of the reducing agent.

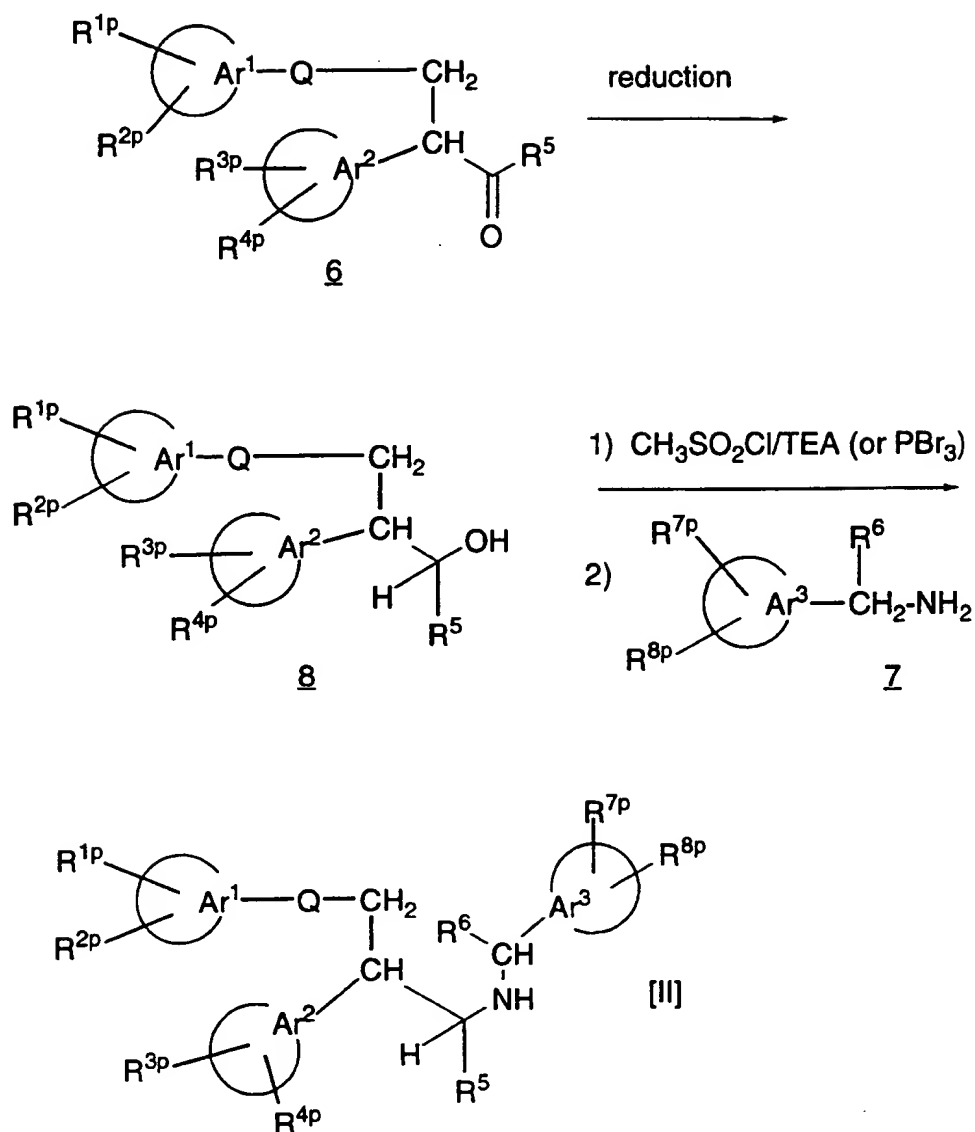
The reaction temperature is usually from 0°C to room temperature, and the reaction time is usually from 1 hour to 6 hours.

Further, in this process, it is also possible to react an alkylating agent of the formula 5 to the nitrile or carboxylic acid derivative of the formula 1 to preliminarily produce an alkyl compound and then to react an alkyl lithium of the formula 2 or an alkyl Grignard reagent (or an alkyl Gilman reagent) of the formula 3 to the alkyl compound to obtain a compound of the formula 6. Such a reaction can be conducted under the conditions similar to the above Process A.

Accordingly, the reaction conditions described for the above Process A may all be used as the reaction conditions for this reaction.

The compounds of the formulas 1, 2, 3, 5 and 7 may be commercially available or can be produced by a proper combination, as the case requires, of the methods disclosed in Examples, or conventional methods or methods similar thereto.

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Process B

- 5 In the above formulas, Ar^1 —, Ar^2 —, Ar^3 —, Q, R^{1p} , R^{2p} , R^{3p} , R^{4p} , R^5 , R^6 , R^{7p} and R^{8p} are as defined above.

According to this process, the desired compound (II) can be prepared by reacting a reducing agent such as a metal hydride complex to a compound of the formula 6 to obtain an alcohol compound 8 and

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reacting an amine compound of the formula 7 to the alcohol compound 8.

The above reaction steps will be described in detail referring to suitable reaction conditions, etc.

5 The reaction for reducing the compound of the formula 6 to the alcohol compound 8 can be conducted usually by using a metal hydride complex such as sodium borohydride, diisobutyl aluminum hydride, lithium aluminum hydride or lithium tri-sec-butylborohydride (L-selectrideTM), or by catalytic reduction employing e.g. a palladium-
10 carbon catalyst or a Raney nickel catalyst, in an inert solvent which does not adversely affect the reaction.

When the metal hydride complex is used as the reducing agent, such a reducing agent is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the
15 starting material compound 6.

The inert solvent to be used in this reaction may be suitably selected depending upon the type of the reducing agent.

For example, when the reducing agent is sodium borohydride, an inert solvent, such as an alcohol such as methanol or
20 ethanol; an ether such as dimethoxyethane, dioxane, tetrahydrofuran or diglyme; an aprotic polar solvent such as dimethylformamide or dimethylacetamide, or water, or a solvent mixture thereof, may be used, and particularly preferred is an alcohol such as methanol or ethanol.

For example, when the reducing agent is diisobutyl
25 aluminum hydride, an inert solvent, such as an ether such as dimethyl ether, ethyl ether, diisopropyl ether, dibutyl ether, dimethoxyethane, dioxane, tetrahydrofuran or diglyme; an aliphatic hydrocarbon such as pentane, hexane, heptane or cyclohexane; an aromatic hydrocarbon such as benzene or toluene; methylene chloride, or a solvent mixture thereof,
30 may be used, and particularly preferred is toluene or methylene chloride.

For example, when the reducing agent is lithium aluminum hydride or lithium tri-sec-butylborohydride, an inert solvent, such as an ether such as dimethyl ether, ethyl ether, diisopropyl ether, dibutyl

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ether, dimethoxyethane, dioxane, tetrahydrofuran or diglyme; an aliphatic hydrocarbon such as pentane, hexane, heptane or cyclohexane; or an aromatic hydrocarbon such as benzene or toluene, or a solvent mixture thereof, may be used, and particularly preferred is ethyl ether or tetrahydrofuran.

For the catalytic reduction, the solvent is preferably an alcohol such as methanol or ethanol.

The reaction temperature and the reaction time vary depending upon the stability and the susceptibility to the reduction reaction of the starting material ketone compound 6, the type of the reducing agent and the type of the solvent. However, the reaction temperature is usually from -80°C to 100°C, preferably from -70°C to 40°C, and the reaction time is usually from 5 minutes to 2 days, preferably from 30 minutes to 24 hours.

The step of preparing the desired compound (II) from a compound of the formula 8 can be carried out by reacting a sulfonating agent such as methanesulfonyl chloride to the alcohol compound of the formula 8 in the presence of a base, or reacting a halogenating agent such as thionyl chloride or phosphorus tribromide thereto, to convert the hydroxyl group in the formula to a leaving group, followed by reacting an amine compound of the formula 7.

The reaction for introducing the leaving group can be conducted usually by reacting 1 mol or an excess molar amount, preferably from 1 to 2 mols, of a sulfonating agent and a base such as triethylamine to 1 mol of the alcohol compound 8 in an inert solvent such as methylene chloride, chloroform, benzene, tetrahydrofuran or ethyl acetate, or using 1 mol or an excess molar amount, preferably from 1 to 5 mols, of a halogenating agent.

The reaction temperature is usually from -70°C to the boiling point of the solvent used for the reaction, preferably from -20°C to 80°C, and the reaction time is usually from 5 minutes to 48 hours, preferably from 30 minutes to 24 hours.

Then, the step of reacting an amine compound 7 to the

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compound having the leaving group introduced, obtained by the above reaction, can be conducted usually by employing 1 mol or an excess molar amount, preferably from 1 to 50 mols, of the amine compound 7 per mol of the starting compound having the leaving group, in an inert solvent such as methylene chloride, chloroform, benzene, ethyl ether or tetrahydrofuran.

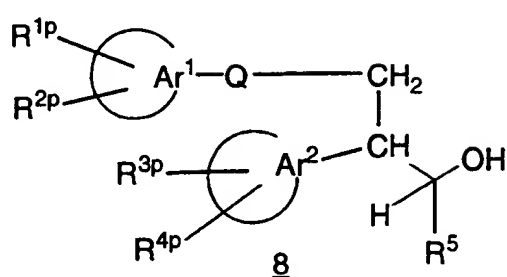
If necessary, this reaction can be conducted in the presence of a base other than the amine compound of the formula 7.

As such a base, an inorganic base such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate or sodium hydrogencarbonate, or an organic base such as triethylamine, N-ethyldiisopropylamine, pyridine or N,N-dimethylaniline may, for example, be mentioned.

Such a base is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the starting material compound.

The reaction temperature is usually from -50°C to 150°C, preferably from -20°C to 100°C, and the reaction time is usually from 5 minutes to 7 days, preferably from 10 minutes to 24 hours.

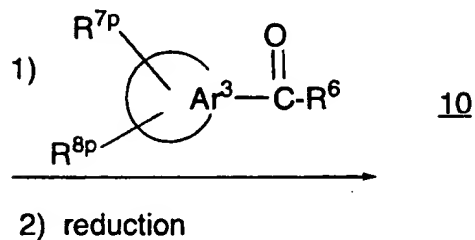
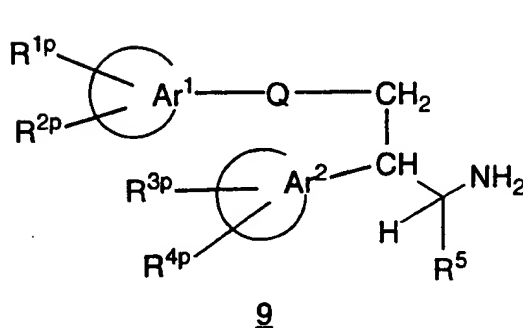
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Process C

1) DEAD, Ph₃P,
Phthalimide (or HN₃ or DPPA)

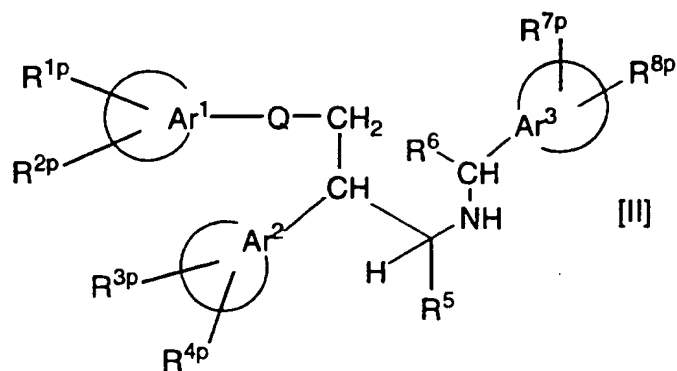
or (i) CH₃SO₂Cl, TEA
ii) Phthalimide (or NaN₃)

2) NH₂NH₂ (or reduction)



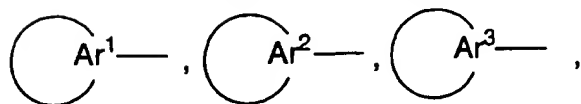
1)

2) reduction



5

In the above formulas,



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Q, R¹P, R²P, R³P, R⁴P, R⁵, R⁶, R⁷P and R⁸P are as defined above.

According to this process, the desired compound (II) can be prepared by firstly reacting diethyl azodicarboxylate, triphenylphosphine and phthalimide (or hydrogen azide or diphenylphosphoryl azide) or reacting a sulfonylation agent such as methanesulfonyl chloride in the presence of a base such as triethylamine, then reacting phthalimide (or sodium azide) in the presence of a base, to the alcohol compound of the formula 8, to obtain a phthalimide-protected form (or an azide compound) of the amine compound 9, then reacting hydrazine (or a reducing agent) to remove the phthalimide group (or reduce the azide group) to obtain an amine product of the formula 9, and finally reacting a compound of the formula 10 to the compound 9, followed by reduction.

The above reaction steps will be described in detail referring to suitable reaction conditions, etc.

For the step of producing the amine compound of the formula 9 from the alcohol compound 8, various synthetic methods and reaction conditions well known in organic synthetic chemistry for converting alcohol compounds to amines, may be employed. For example, it is preferred to employ a Mitsunobu reaction using diethyl azodicarboxylate, triphenylphosphine and phthalimide (or hydrogen azide or diphenylphosphoryl azide) or a method which comprises sulfonylation with a sulfonylation agent such as methanesulfonyl chloride in the presence of a base such as triethylamine, then reacting phthalimide (or sodium azide) in the presence of a base, and then treating the obtained phthalimide compound with hydrazine (or reducing the azide compound).

The above reactions are conducted usually in a solvent inert to the reaction. The inert solvent may, for example, preferably be tetrahydrofuran, dimethoxyethane, benzene or toluene in the case of the above-mentioned Mitsunobu reaction; methylene chloride, chloroform, tetrahydrofuran, benzene, ethyl acetate or dimethylformamide in the case of the sulfonylation followed by the

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reaction with phthalimide (or sodium azide); an alcohol such as methanol or ethanol in the next step of the phthalimide-removing reaction with hydrazine; an ether such as ethyl ether or tetrahydrofuran in the case where a metal hydride complex is used as the reducing agent
5 in the reduction reaction of the azide compound; water-containing tetrahydrofuran in the case where phosphine reduction is conducted with triphenylphosphine or the like; and an alcohol such as methanol or ethanol in the reduction by catalytic reduction.

With respect to the amounts of the reagents to be used, in
10 the above Mitsunobu reaction, each of diethyl azodicarboxylate, triphenylphosphine and phthalimide (or hydrogen azide or diphenylphosphoryl azide) is used in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the starting material alcohol compound 8. In the reaction with the phthalimide (or
15 sodium azide) after the sulfonylation, the sulfonylation agent such as methanesulfonyl chloride is used in an amount of 1 mol or an excess molar amount, preferably from 1 to 2 mols, per mol of the alcohol compound 8, and the base such as triethylamine used at that time is usually in an amount of 1 mol or an excess molar amount, preferably
20 from 1 to 2 mols, per mol of the sulfonylation agent. In the next step of the reaction with phthalimide (or sodium azide) in the presence of a base, 1 mol or an excess molar amount, preferably from 1 to 5 mols of each of phthalimide and the base (or sodium azide) is used per mol of the starting material sulfonylation agent. Here, the base to be used
25 together with phthalimide is preferably sodium carbonate or potassium carbonate. Otherwise, without using such a base, a sodium salt or a potassium salt of phthalimide may be used by itself. Then, in the reaction for removing the phthalimide group with hydrazine, hydrazine is used in an amount of 1 mol or an excess molar amount, preferably
30 from 1 to 10 mols, per mol of the phthalimide compound as the starting material compound. In the reduction of the azide compound with a metal hydride complex or with triphenylphosphine, the reducing agent is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 2 mols, per mol of the azide compound.

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In the case of the above Mitsunobu reaction, the reaction temperature is usually from -70°C to 100°C , preferably from -20°C to 50°C , and the reaction time is usually from 5 minutes to 48 hours, preferably from 30 minutes to 24 hours. In the reaction for removing the phthalimide group by hydrazine, the reaction temperature is usually from 0°C to the boiling point of the solvent used for the reaction, preferably from room temperature to 100°C , and the reaction time is usually from 5 minutes to 48 hours, preferably from 30 minutes to 24 hours. In the reaction for converting the azide compound to the amine compound by reduction, when a metal hydride complex is used as the reducing agent, the reaction temperature is usually from -70°C to 150°C , preferably from -20°C to 50°C , and the reaction time is usually from 5 minutes to 48 hours, preferably from 10 minutes to 10 hours. When triphenylphosphine is used as the reducing agent, the reaction temperature is usually from room temperature to the boiling point of the solvent used for the reaction, preferably from 30°C to 100°C , and the reaction time is usually from 10 minutes to 48 hours, preferably from 30 minutes to 24 hours. Further, in the case of the reduction by catalytic reduction, the reaction temperature is usually from 0°C to 100°C , preferably from room temperature to 50°C , and the reaction time is usually from 10 minutes to 48 hours, preferably from 10 minutes to 24 hours.

The step for producing the desired compound (II) from the compound of the formula 9 is carried out usually by preliminarily forming an imine by reacting 1 mol or an excess molar amount, preferably from 1 to 2 mols of the compound of the formula 10 to 1 mol of the compound of the formula 9 in an inert solvent such as methanol, ethanol, benzene, ethyl ether or tetrahydrofuran, and then reducing it.

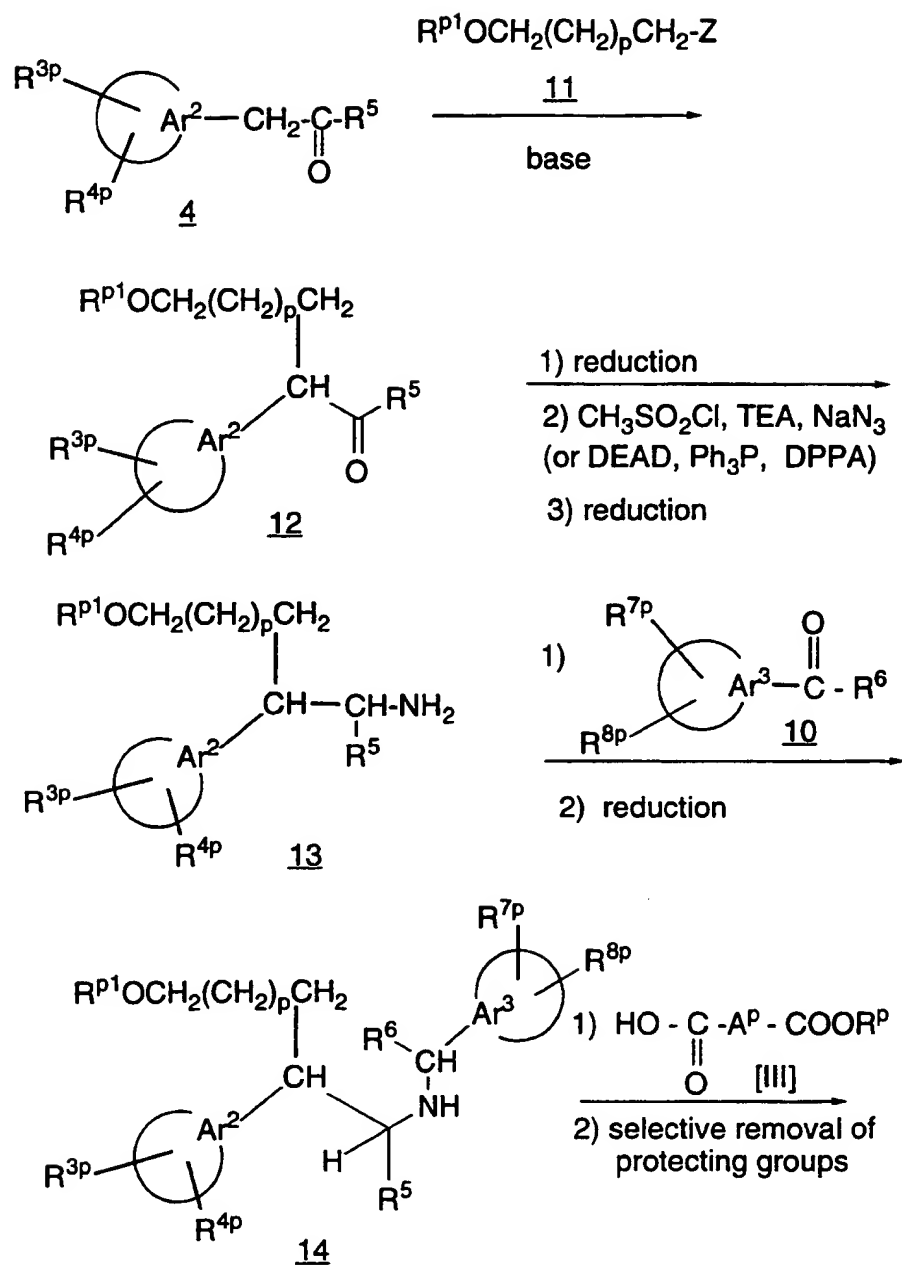
This step can be carried out in the same manner as the step for producing the desired compound (II) from the compound of the formula 6 in the above process A. Accordingly, with respect to the reaction conditions, etc., similar modes may be employed.

Further, the compound of the formula 10 may be

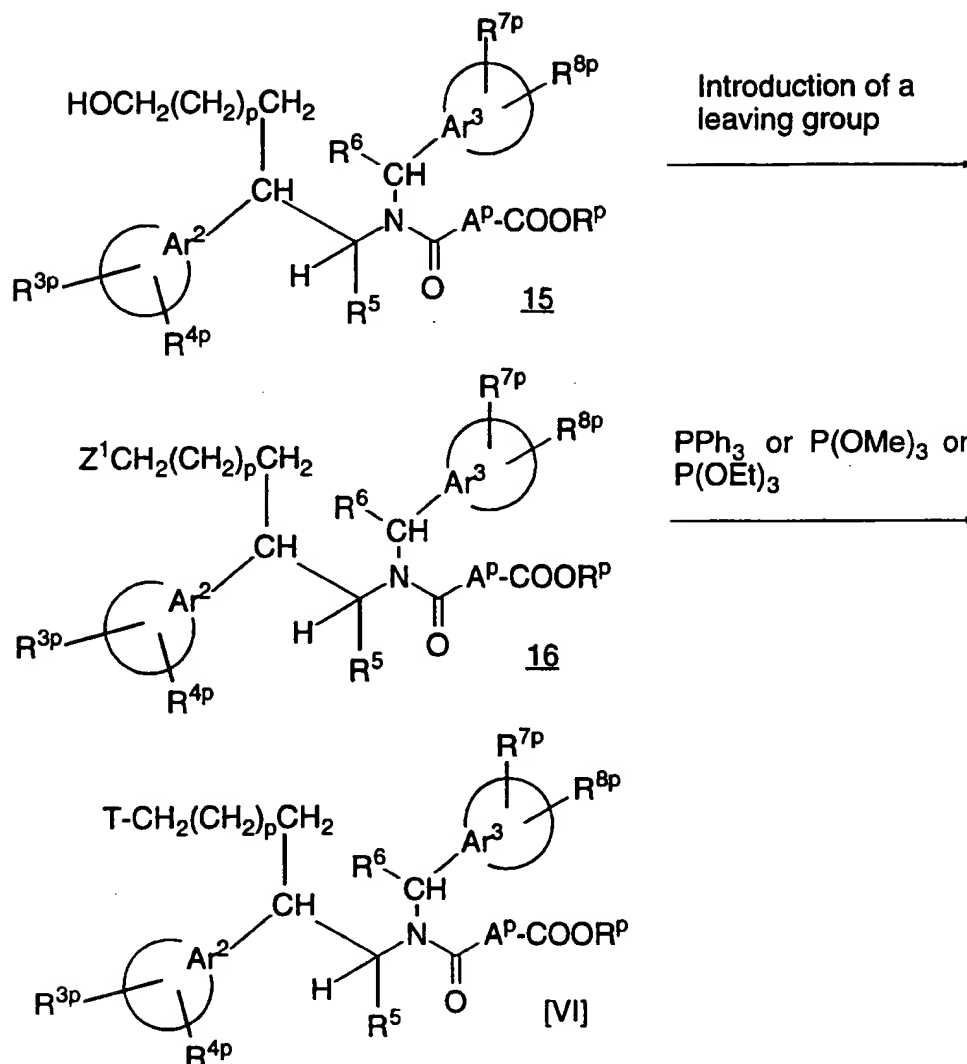
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commercially available or can be produced by a proper combination, as the case requires, of the methods disclosed in Examples, or conventional methods or methods similar thereto.

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Process D

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In the above formulas, R^{1p} means a hydroxyl-protecting group;

and $\bigcirc \text{Ar}^2 -$, $\bigcirc \text{Ar}^3 -$, AP, p, T, Z, Z¹, R³p, R⁴p, R⁵, R⁶, R⁷p, R⁸p and RP are as defined above.

5 According to this process, the desired compound (VI) can be prepared by firstly reacting an alkylating agent of the formula 11 to a ketone compound of the formula 4 to obtain a compound of the formula 12, reacting a reducing agent such as a metal hydride complex to the compound 12 to obtain an alcohol compound, then reacting
10 diethyl azodicarboxylate, triphenylphosphine and phthalimide (or

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hydrogen azide or diphenylphosphoryl azide) or reacting a sulfonylation agent such as methanesulfonyl chloride in the presence of a base such as triethylamine, and then reacting phthalimide (or sodium azide) in the presence of a base, to obtain a phthalimide-protected form (or an azide compound) of the amine compound 13, then reacting hydrazine (or a reducing agent) to remove the phthalimide group (or reduce the azide group) to obtain an amine compound of the formula 13, reacting a compound of the formula 10 to the compound 13, followed by reduction to obtain a compound of the formula 14, reacting a carboxylic acid of the formula (III) or its reactive derivative to the compound 14, then selectively removing the protecting group represented by RP^1 to obtain a compound of the formula 15, then introducing a leaving group to the compound 15 to obtain a compound of the 16, and finally reacting triphenylphosphine, trimethyl phosphite or triethyl phosphite to the compound 16.

The hydroxyl-protecting group of RP^1 may be the hydroxyl-protecting groups mentioned above with respect to process 1.

The step of producing a compound of the formula 12 from a ketone compound of the formula 4, can be carried out in the same manner as the step of producing the compound of the formula 6 from the ketone of the formula 4 in the above process A. Accordingly, with respect to the reaction conditions, etc., similar conditions may be employed.

In the step of producing the amine compound of the formula 13 after reacting a reducing agent such as a metal hydride complex to the compound of the formula 12 to obtain an alcohol compound, the step of converting the compound of the formula 12 to the alcohol compound can be carried out in the same manner as the step of reducing the compound of the formula 6 to the alcohol compound 8 in the above process B. Accordingly, with respect to the reaction conditions, etc., similar conditions may be employed. Further, the step of producing an amine compound of the formula 13 from the obtained alcohol, can be carried out in the same manner as in the step of producing the amine compound 9 from the alcohol compound of the

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formula 8 in the above process C. Accordingly, with respect to the reaction conditions, etc., similar conditions may be employed.

5 The step of producing a compound of the formula 14 from the amine compound of the formula 13, can be carried out in the same manner as in the step of producing a compound of the formula (II) from the amine of the formula 2 in the above process C. Accordingly, with respect to the reaction conditions, etc., similar conditions may be employed.

10 In the step of producing a compound of the formula 15 from the compound of the formula 14, the reaction of the compound of the formula 14 with the carboxylic acid of the formula (III) or its reactive derivative, can be carried out in the same manner as the reaction of the compound of the formula (II) with the carboxylic acid of the formula (III) or its reactive derivative in the above process
15 1. Accordingly, with respect to the reaction conditions, etc., similar conditions may be employed.

For the step of selectively removing the protective group represented by RP^1 from the compound obtained by the above reaction, various methods may suitably be selected depending upon the type and
20 the characteristics of the protecting group. Namely, utilizing the difference in the stability against an acid, a base or reduction between RP^1 and other protecting groups, the protecting group can selectively be removed by a conventional means such as an acid, a base or reduction. With respect to specific conditions for such a reaction, the methods
25 disclosed in known literatures, such as "Protective Groups in Organic Synthesis, T.W. Greene, John Siley & Sons (1981)", may, for example, be used.

30 The step of producing a compound of the formula 16 by introducing a leaving group to the compound of the formula 15 can be carried out in the same manner as in the method of introducing a leaving group to the compound of the formula 8 in the above process B by using, for example, a halogenating agent such as thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, phosphorus tribromide, oxalyl chloride or phosgene, or a

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sulfonating agent such as methanesulfonyl chloride, p-toluenesulfonyl chloride or benzenesulfonyl chloride. Accordingly, with respect to the reaction conditions, etc., similar conditions may be employed.

5 The step of producing the desired compound (VI) from the compound of the formula 16, can be carried out by reacting triphenylphosphine, trimethyl phosphite or triethyl phosphite, to the compound of the formula 16.

When a triphenylphosphine is reacted, the above reaction is carried out usually in an inert solvent which does not affect the reaction.
10 As such an inert solvent, toluene or xylene is, for example, preferred.

The triphenylphosphine is used usually in an amount of 1 mol or an excess molar amount, preferably from 1 to 5 mols, per mol of the compound 16.

The reaction temperature is usually from room
15 temperature to the boiling point of the solvent used for the reaction, preferably from 80°C to 150°C. The reaction time is usually from 5 minutes to 7 days, preferably from 1 hour to 24 hours.

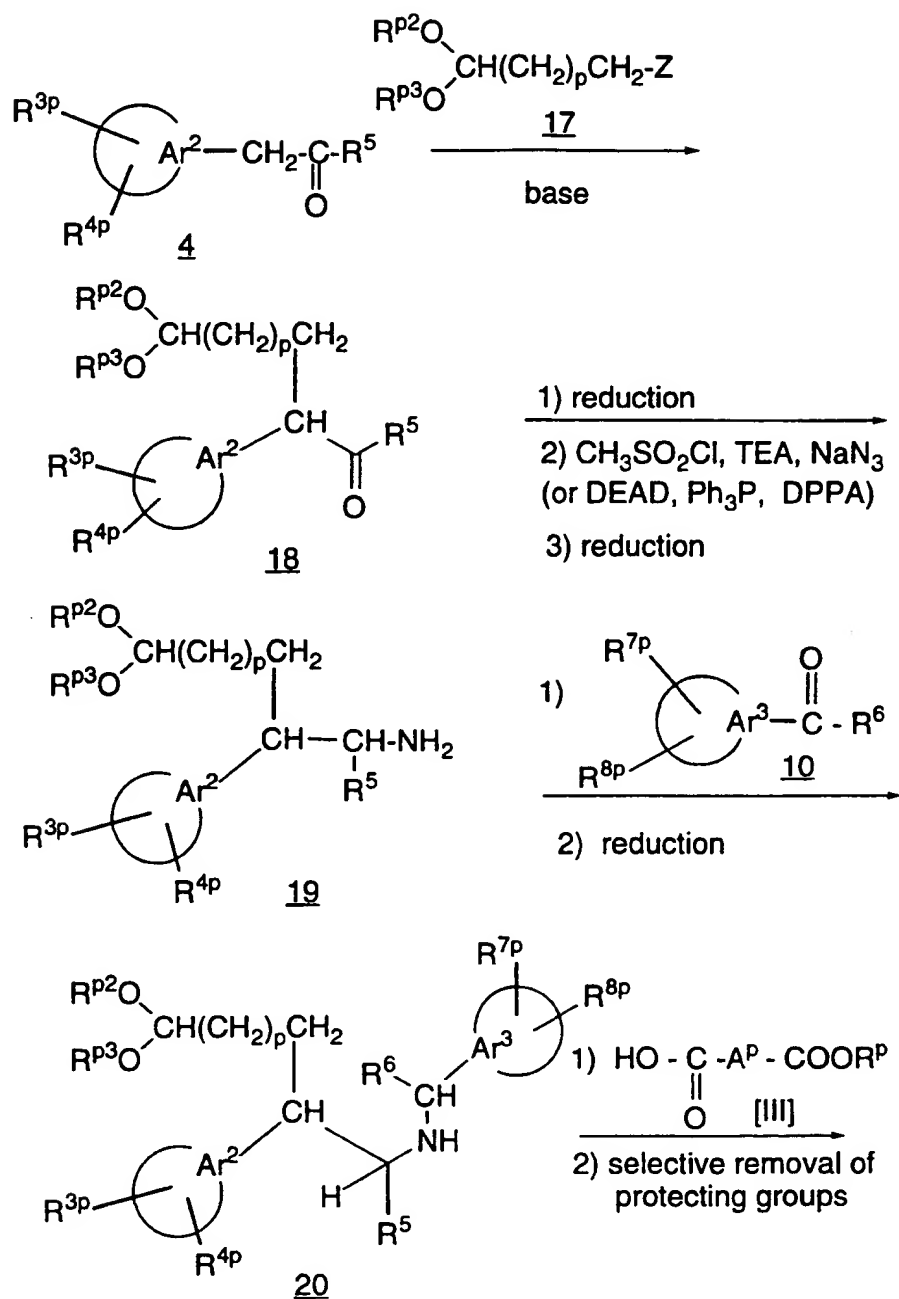
Likewise, when trimethyl phosphite or triethyl phosphite is reacted to the compound 16, the above reaction is conducted
20 usually in an inert solvent which does not affect the reaction, or more preferably, an excess trimethyl phosphite or triethyl phosphite is used as both the solvent and the reactant.

The reaction temperature is usually from room temperature to the boiling point of the solvent for the reaction, preferably from
25 80°C to 150°C, and the reaction time is usually from 5 minutes to 7 days, preferably from 1 hour to 24 hours.

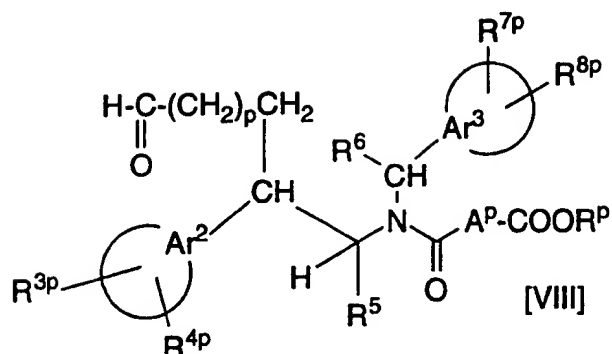
Further, the compound of the formula 11 may be commercially available, or may be produced by a proper combination, as the case requires, of the methods disclosed in Examples, or
30 conventional methods or methods similar thereto.

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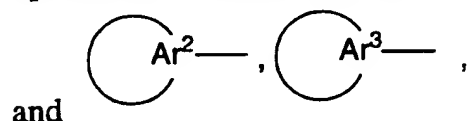
Process E



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In the above formulas, each of RP^2 and RP^3 which are the same or different, is a methyl group or an ethyl group, or RP^2 and RP^3 together represent an ethylene group;



AP , p , Z , R^{3p} , R^{4p} , R^5 , R^6 , R^{7p} , R^{8p} and RP are as defined above.

According to this process, the desired compound (VIII) can be prepared by firstly reacting an alkylating agent of the formula 17 to a ketone compound of the formula 4 to obtain a compound of the formula 18, reacting a reducing agent such as a metal hydride complex to the compound 18 to obtain an alcohol compound, then reacting diethyl azodicarboxylate, triphenylphosphine and phthalimide (or hydrogen azide or diphenylphosphoryl azide), or reacting a sulfonylation agent such as methanesulfonyl chloride in the presence of a base such as triethylamine and then reacting phthalimide (or sodium azide) in the presence of a base, to obtain a phthalimide-protected form (or an azide compound) of the amine compound 19, then reacting hydrazine (or a reducing agent) to remove the phthalimide group (or reduce the azide group) to obtain an amine compound of the formula 19, reacting a compound of the formula 10 to the compound 19, followed by reduction to obtain a compound of the formula 20, reacting a carboxylic acid of the formula (III) or its reactive derivative to the compound 20, and then selectively removing the protecting groups represented by RP^2 and RP^3 .

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Removal of such protecting groups is usually preferably conducted in the presence of an acid such as hydrochloric acid, sulfuric acid or p-toluenesulfonic acid in a solvent such as water-containing methanol, water-containing ethanol or water-containing tetrahydrofuran.

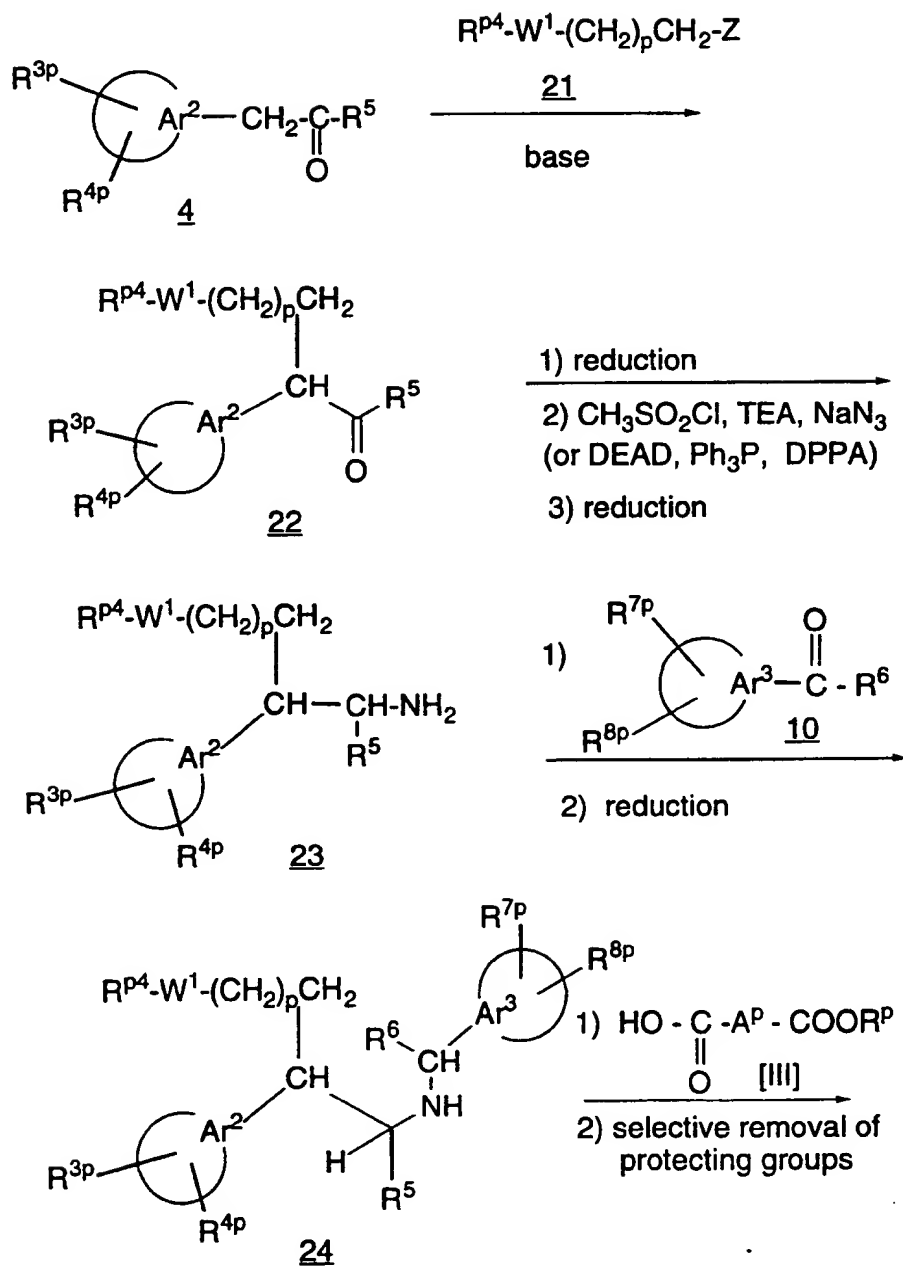
The reaction temperature is usually from -20°C to 100°C, preferably from 0°C to 50°C, and the reaction time is usually from 5 minutes to 48 hours, preferably from 10 minutes to 24 hours.

The respective steps up to the production of the desired compound (VIII) from the ketone compound of the formula 4 can be carried out in the same manner as the respective steps for the production of the compound of the formula 15 from the ketone compound of the formula 4 in the above process D. Accordingly, with respect to the reaction conditions, etc., the same conditions as in the corresponding respective steps can be employed.

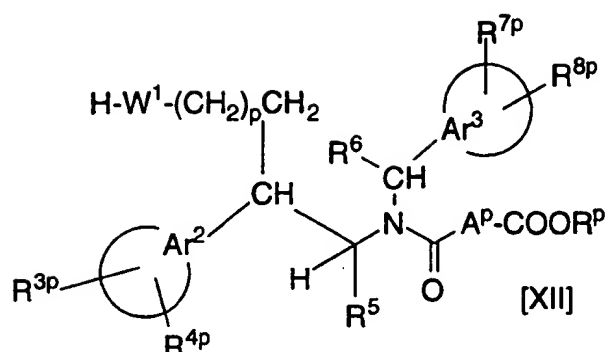
Further, the compound of the formula 17 may be commercially available, or can be produced by a proper combination, as the case requires, of the methods disclosed in Examples, or conventional methods or methods similar thereto.

20

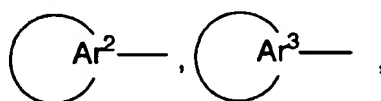
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Process F

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- 5 In the above formulas, RP^4 represents a hydroxyl-protecting group when W^1 is an oxygen atom; or a mercapto-protecting group when W^1



is a sulfur atom; and

$AP, p, W^1, Z, R^{3p},$

$R^{4p}, R^5, R^6, R^{7p}, R^{8p}$ and RP are as defined above.

- According to this process, the desired compound (XII) can be prepared by firstly reacting an alkylating agent of the formula 21 to a ketone compound of the formula 4 to obtain a compound of the formula 22, reacting a reducing agent such as a metal hydride complex to the compound 22 to obtain an alcohol compound, then reacting diethyl azodicarboxylate, triphenylphosphine and phthalimide (or hydrogen azide or diphenylphosphoryl azide), or reacting a
- 15 sulfonylation agent such as methanesulfonyl chloride in the presence of a base such as triethylamine and then reacting phthalimide (or sodium azide) in the presence of a base, to obtain a phthalimide-protected form (or an azide compound) of the amine compound 23, then reacting hydrazine (or a reducing agent) to remove the phthalimide group (or
- 20 reduce the azide group) to obtain an amine of the formula 23, reacting a compound of the formula 10 to the compound 23, followed by reduction to obtain a compound of the formula 24, reacting a carboxylic acid of the formula (III) or its reactive derivative to the compound 24, and then selectively removing the protecting group represented by RP^4 .

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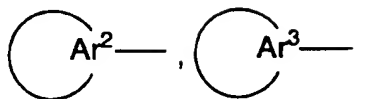
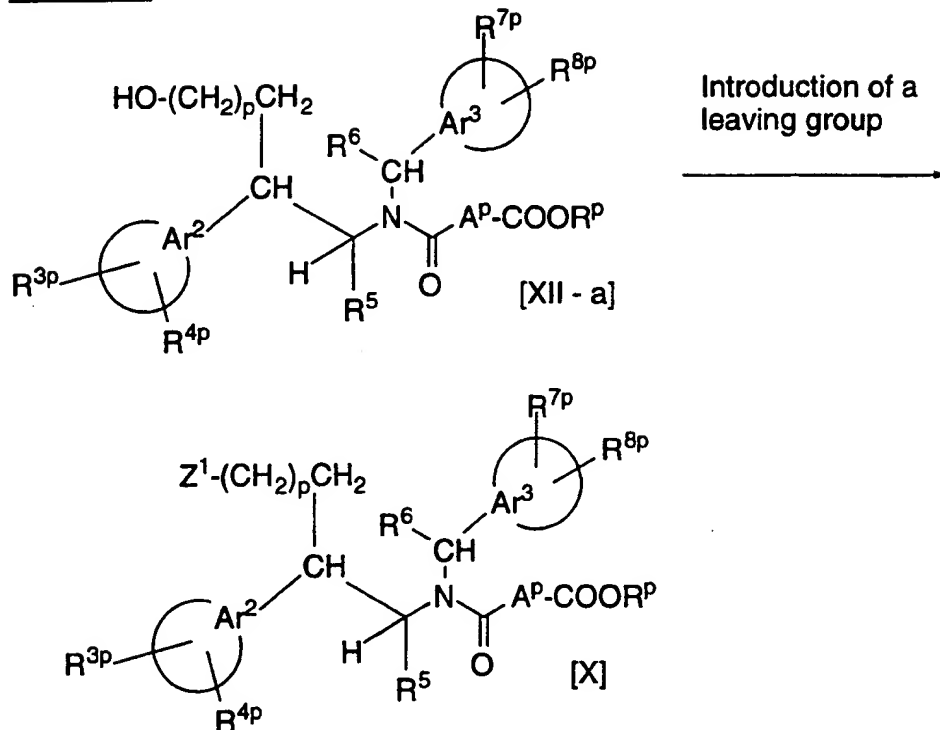
When RP^4 is a hydroxyl-protecting group, as such a hydroxyl-protecting group, the hydroxyl-protecting groups disclosed above with respect to process 1 may be employed.

5 When RP^4 is a mercapto-protecting group, as such a mercapto-protecting group, the hydroxyl-protecting groups disclosed above with respect to process 1 can be employed.

The respective steps up to the production of the desired compound (XII) from the ketone compound of the formula 4 can be carried out in the same manner as the respective steps for the production
10 of the compound of the formula 15 from the ketone compound of the formula 4 in the above process D. Accordingly, with respect to the reaction conditions, etc., the same conditions as in the corresponding respective steps can be employed.

15 Further, the compound of the formula 21 may be commercially available, or can be produced by a proper combination, as the case requires, of the methods disclosed in Examples, or conventional methods or methods similar thereto.

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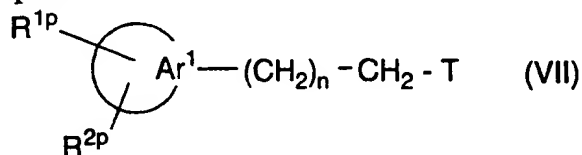
Process G

- In the above formulas, AP, p, Z1, R3p, R4p, R5, R6, R7p, R8p and RP are as defined above.

According to this process, the desired compound (X) can be prepared by introducing a leaving group to the compound of the formula (XII-a).

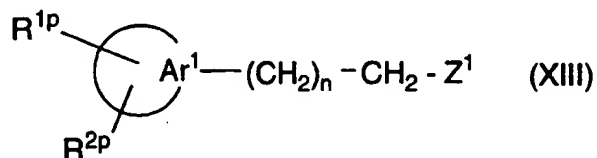
- This step can be carried out in the same manner as the method of introducing a leaving group to the compound of the formula 15 in the above process D. Accordingly, with respect to the reaction conditions, etc., similar conditions may be employed.

A compound of the formula (VII):



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wherein $\bigcirc\text{Ar}^1-$, n , T , R^{1p} and R^{2p} are as defined above, can be prepared from a compound of the formula (XIII):

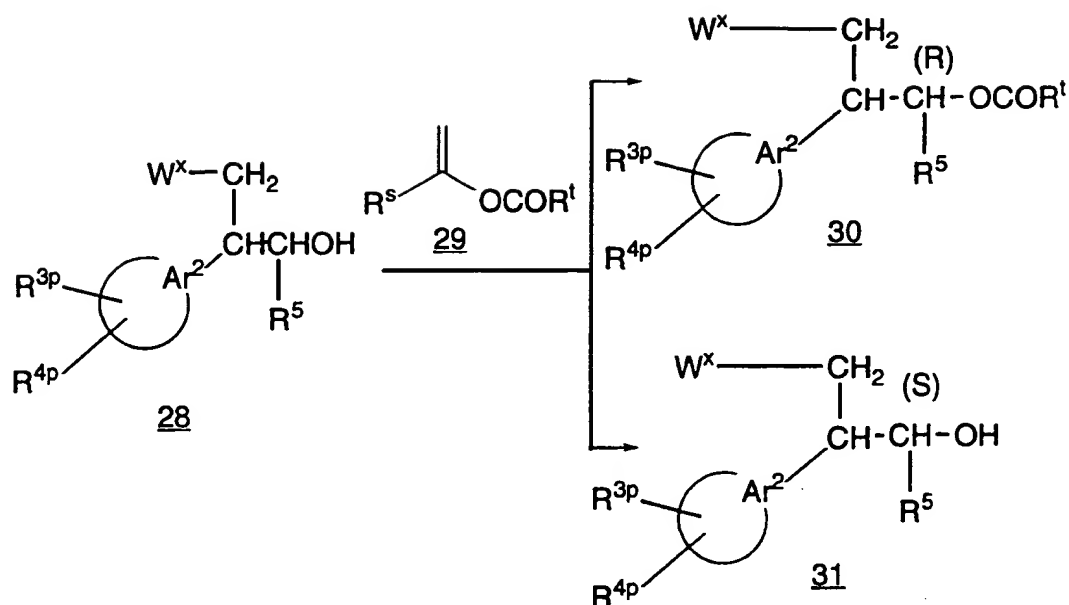


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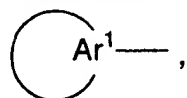
wherein $\bigcirc\text{Ar}^1-$, n , Z^1 , R^{1p} and R^{2p} are as defined above, in accordance with the method for producing a compound of the formula (VI) from the compound of the formula 16 in process D.

10 Further, the compound of the formula (XIII) may be commercially available, or can be prepared by a proper combination, as the case requires, of the methods disclosed in Examples, or conventional methods or methods similar thereto.

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Process H

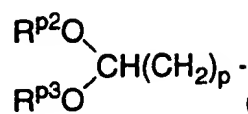
5 In the above formulas, W^x is



Q , R^{1p} and R^{2p} are as defined above),

$RP^4-W^1-(CH_2)^{p'}$ - (wherein p' is an integer of from 0 to 4; and RP^4 and W^1 are as defined above) or

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(wherein $\text{R}^{\text{p}2}$, $\text{R}^{\text{p}3}$ and p are as defined above); R^{s} is a hydrogen atom or a methyl group; R^{t} is a lower alkyl group, an aryl

group or a lower alkenyl group; and Ar^2 —, R^{3p} , R^{4p} and R^{5} are as defined above.

5 Process H is a process for preparing an optically active substance 31 or 32 of an alcohol compound 28 obtainable as the above formula 8 or a reduction product of the formula 12, 18 or 22.

10 According to this process, the desired optically active alcohol compounds 31 and 32 can be prepared by reacting a vinyl ester derivative of the formula 29 to a racemic alcohol derivative of the formula 28 in the presence of a lipase, separating the obtained optically active ester derivative 30 and the optically active alcohol derivative, and then hydrolyzing the ester group with respect to the optically active ester derivative 30.

15 R^{t} of the vinyl ester derivative of the formula 29 is preferably a lower alkyl group such as a methyl group or an ethyl group; an aryl group such as a phenyl group or a naphthyl group; or an aralkyl group such as a benzyl group or a 2-phenylethyl group. Particularly preferred is a methyl group, i.e. a case wherein the
20 compound of the formula 29 is vinyl acetate or isopropenyl acetate.

25 The above optical resolution reaction by lipase can be conducted usually in an inert solvent such as methylene chloride, chloroform, ethyl ether, tetrahydrofuran, benzene, toluene, hexane, heptane or acetonitrile, or by using the starting material vinyl ester derivative of the formula 29 itself as the solvent.

30 The vinyl ester derivative 29 is used usually in an amount of 1 mol or in a large excess molar amount, preferably from 1 to 100 mols, per mol of the starting material compound 28, and the amount of the lipase as the catalyst is from 0.01 to 100% preferably from 0.1 to 20%, by weight, relative to the compound 28.

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The type of the lipase is preferably a lipase derivative from *Pseudomonas* sp. such as Toyothium LIP™ (manufactured by Toyobo).

Further, the above enzymatic reaction tends to be accelerated, when the reaction is carried out in the presence of a base.

5 As a base to be used for this purpose, an organic base such as triethylamine or diisopropylethylamine, is preferred.

The base is used usually in an amount of 0.01 mol or slightly excess molar amount, preferably from 0.1 to 1.5 mols, relative to the starting material compound 28.

10 The reaction temperature is usually from 0°C to 50°C, preferably from room temperature to 40°C. The reaction time is usually from 30 minutes to 7 days, preferably from 1 hour to 48 hours.

The hydrolytic reaction of the ester of the formula 30 can be conducted by a common method well known in the
15 organic synthetic chemistry under an acidic or basic condition.

The compositions of this invention inhibit Ras farnesyl transferase which catalyzes the first step in the post-translational
20 processing of Ras and the biosynthesis of functional Ras protein. These compositions are useful as pharmaceutical agents for mammals, especially for humans. These compositions may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compositions of this invention
25 include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias.

The compositions of this invention are also useful for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation
30 in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compositions of the invention to a mammal in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which the

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Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn) may be inhibited by the compositions of this invention.

In practicing the methods of this invention, which comprise
5 administering, simultaneously or sequentially or in any order, two or more of a protein substrate-competitive inhibitor and a farnesyl pyrophosphate-competitive inhibitor, such administration can be orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of
10 administration. It is preferred that such administration be orally. It is more preferred that such administration be orally and simultaneously. When the protein substrate-competitive inhibitor and farnesyl pyrophosphate-competitive inhibitor are administered sequentially, the administration of each can be by the same method or by different
15 methods.

The compositions of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical
20 composition, according to standard pharmaceutical practice.

For oral use of a chemotherapeutic composition according to this invention, the selected composition may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are
25 commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents.
30 If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For

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intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and
5 pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's intramuscular blood-stream by local bolus injection.

When a composition according to this invention is administered into a human subject, the daily dosage will normally be
10 determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of composition is administered to a mammal undergoing treatment for
15 cancer. Administration occurs in an amount of a composition that comprises between about 0.1 mg/kg of body weight to about 40 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 20 mg/kg of body weight per day of a protein substrate-competitive inhibitor and an amount between about 0.1 mg/kg of body
20 weight to about 40 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 20 mg/kg of body weight per day of a farnesyl pyrophosphate-competitive inhibitor.

EXAMPLES

25

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

30

EXAMPLE 1

Preparation of N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-2-naphthylmethylamine

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(1) Preparation of (E)-3-(4-chlorophenyl)-6-(2-naphthyl)-5-hexen-2-one

2.56 g of p-chlorophenylacetone was dissolved in a mixed solution of 5 ml of dimethylformamide and 5 ml of benzene, and a
5 dimethylformamide 8 ml/benzene 8 ml solution containing 0.62 g of 60% oily sodium hydride and 3.50 g of (E)-3-(2-naphthyl)-2-propenyl bromide, was added under cooling with ice with stirring, followed by stirring at room temperature for 2 hours. The reaction solution was acidified by an addition of 1N hydrochloric acid and extracted by an
10 addition of water and ethyl ether. Then, the organic layer was washed with a saturated sodium chloride aqueous solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate
15 5/1) to obtain the above-identified compound.

(2) Preparation of (2RS,3SR,5E)-3-(4-chlorophenyl)-6-(2-naphthyl)-5-hexen-2-ol

4.78 g of (E)-3-(4-chlorophenyl)-6-(2-naphthyl)-5-hexen-
20 2-one was dissolved in 30 ml of tetrahydrofuran, and 14.3 ml of a 1M tetrahydrofuran solution of lithium tri-sec-butyl borohydride was added at -78°C under cooling with stirring, followed by stirring at the same temperature for 2 hours. To the reaction solution, 10 ml of a 2N sodium hydroxide aqueous solution was added under cooling with ice
25 with stirring, and then, 15 ml of a 30% hydrogen peroxide aqueous solution was gradually dropwise added, followed by stirring at room temperature for one hour. The reaction solution was extracted by an addition of ethyl ether and water. The organic layer was washed with a saturated sodium thiosulfate aqueous solution and a saturated sodium
30 chloride aqueous solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 15/1 to 5/1) to obtain the above-identified

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compound.

(3) Preparation of (1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-
5-(2-naphthyl)-4-pentenylamine

5 4.06 g of (2RS,3SR,5E)-3-(4-chlorophenyl)-6-(2-naphthyl)-
5-hexen-2-ol was dissolved in 30 ml of tetrahydrofuran, and 4.77 g of
triphenylphosphine, 2.89 ml of diethyl azodicarboxylate and 4.77 g of
diphenylphosphoryl azide were added under cooling with ice with
stirring, followed by stirring at room temperature for 30 minutes. The
10 reaction solution was evaporated to dryness under reduced pressure.
Then, the residue was purified by silica gel column chromatography
(hexane/ethyl acetate = 50/1 to 30/1). The obtained azide product was
heated and refluxed together with 3.2 g of triphenylphosphine in 100 ml
of 10% water-containing tetrahydrofuran. The reaction solution was
15 evaporated to dryness under reduced pressure. Then, the residue was
purified by silica gel column chromatography (methylene
chloride/methanol = 50/1 to 20/1) to obtain the above-identified
compound.

20 (4) Preparation of N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-
methyl-5-(2-naphthyl)-4-pentenyl}-2-naphthylmethylamine
0.75 g of (1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-
naphthyl)-4-pentenylamine was dissolved in 10 ml of methanol, and 0.34
g of 2-naphthoaldehyde was added thereto, followed by stirring at room
25 temperature overnight. To the reaction solution, 10 mg of
tetrahydrofuran was added to dissolve the formed precipitate, and 84
mg of sodium borohydride was added thereto, followed by stirring at
room temperature for 2 hours. The reaction solution was extracted by
an addition of ethyl ether and water. The organic layer was washed
30 with a saturated sodium chloride aqueous solution and then dried over
anhydrous magnesium sulfate. The drying agent was filtered off, and
then, the solvent was distilled off under reduced pressure. The residue
was purified by silica gel column chromatography (hexane/ethyl acetate
= 7/1 to 3/1) to obtain the above-identified compound.

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The reaction was carried out in the same manner as in Example 1 except that instead of the p-chlorophenylacetone and/or (E)-3-(2-naphthyl)-2-propenylbromide and/or 2-naphthoaldehyde, used as the starting material in the above reaction, the corresponding arylacetone derivative and/or halide and/or arylaldehyde derivative, was used to obtain N{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(1-naphthyl)-4-pentenyl}-2-naphthylmethylamine, N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentyl}-2-naphthylmethylamine, N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-4-(2-naphthoxy)butyl}-2-naphthylmethylamine, N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-4-(2-naphthyl)butyl}-2-naphthylmethylamine, N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-6-(2-naphthyl)hexyl}-2-naphthylmethylamine, N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-5-phenyl-4-pentynyl}-2-naphthylmethylamine, N-{(1RS,2RS,4E)-2-(4-methoxyphenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-2-naphthylmethylamine, N-{(1RS,2RS,4E)-2-(4-methylphenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-2-naphthylmethylamine, N-{(1RS,2RS,4E)-1-methyl-5-(2-naphthyl)-2-(4-nitrophenyl)-4-pentenyl}-2-naphthylmethylamine, N-{(1RS,2RS,4E)-2-(4-fluorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-2-naphthylmethylamine, N-{(1RS,2RS,4E)-1-methyl-5-(2-naphthyl)-2-(4-trifluoromethylphenyl)-4-pentenyl}-2-naphthylmethylamine, N-{(1RS,2RS,4E)-1-methyl-5-(2-naphthyl)-2-phenyl-4-pentenyl}-2-naphthylmethylamine, N-{(1RS,2RS,4E)-1-methyl-2-(6-methyl-3-pyridyl)-5-(2-naphthyl)-4-pentenyl}-2-naphthylmethylamine, N-{(1RS,2RS,6E)-2-(4-chlorophenyl)-1-methyl-7-phenyl-6-heptenyl}-2-naphthylmethylamine, N-{(1RS,2RS,6E)-2-(4-chlorophenyl)-1-methyl-7-(2-naphthyl)-6-heptenyl}-2-naphthylmethylamine, N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-3-quinolylmethylamine, N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-3,4-difluorobenzylamine, N-(2-benzoxazolylmethyl)-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}amine, N-(2-benzo[b]thienylmethyl)-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-

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- (2-naphthyl)-4-pentenyl} amine, N-{(1RS,2RS,4E)-1-methyl-2-(3,4-methylenedioxyphenyl)-5-(2-naphthyl)-4-pentenyl}-2-naphthylmethylamine, N-{(1RS,2RS)-4,4-diethoxy-1-methyl-2-(3,4-methylenedioxyphenyl)butyl}-2-naphthylmethylamine, N-(2-benzo[b]furanylmethyl)-{(1RS,2RS)-4,4-diethoxy-1-methyl-2-(3,4-methylenedioxyphenyl)butyl} amine, N-(2-benzo[b]thienylmethyl)-{(1RS,2RS)-4,4-diethoxy-1-methyl-2-(3,4-methylenedioxyphenyl)butyl} amine, N-[(1RS,2RS)-4,4-diethoxy-1-methyl-2-[(3,4-bis(methoxycarbonyl)phenyl)butyl]-2-naphthylmethylamine, N-(2-benzo[b]thienylmethyl)-{(1RS,2RS)-4,4-diethoxy-2-(4-methoxycarbonylphenyl)-1-methylbutylamine, N-(2-benzo[b]furanylmethyl)-{(1RS,2RS)-4,4-diethoxy-2-(4-methoxycarbonylphenyl)-1-methylbutyl} amine, N-(2-benzo[b]thienylmethyl)-{(1RS,2RS)-2-(4-cyanophenyl)-4,4-diethoxy-1-methylbutyl} amine, N-(5-benzo[b]thienylmethyl)-{(1RS,2RS)-4,4-diethoxy-2-(4-methoxycarbonylphenyl)-1-methylbutyl} amine, N-[(1RS,2RS)-2-(4-chlorophenyl)-4,4-diethoxy-1-methylbutyl]-2-naphthylmethylamine, N-[(1RS,2RS)-2-(4-cyanophenyl)-4,4-diethoxy-1-methylbutyl]-2-naphthylmethylamine, N-[(1RS,2RS)-2-(4-cyanophenyl)-4,4-diethoxy-1-methylbutyl]-2-naphthylmethylamine, N-[(1RS,2RS)-2-(4-methoxycarbonylphenyl)-1-methylbutyl]-2-naphthylmethylamine, N-[(1RS,2RS,4E)-2-(4-methoxycarbonylphenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl]-2-naphthylmethylamine and N-[(1RS,2RS)-5-(1,3-dioxolan-2-yl)-1-methyl-2-(3,4-methylenedioxyphenyl)butyl]-2-naphthylmethylamine.

EXAMPLE 2

- Preparation of 1,2-di-tert-butyl 1, 2, 3-propanetricarboxylate and its optical resolution

- 13.1 ml of a 1.5M cyclohexane solution of lithium diisopropylamide was dissolved in 10 ml of tetrahydrofuran, and a tetrahydrofuran solution (10 ml) containing 2.96 g of benzyl acetate was added under cooling to -70°C with stirring, followed by stirring at the

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same temperature for 30 minutes. Then, a tetrahydrofuran solution (10 ml) containing 2.96 g of di-tert-butyl maleate, was dropwise added thereto, followed by stirring at the same temperature for 30 minutes. The reaction solution was extracted by an addition of 20 ml of water and 50 ml of ethyl ether. The organic layer was separated, then washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the solvent was distilled off under reduced pressure. The residue was dissolved in 50 ml of dioxane, and 0.4 g of a 10% palladium carbon catalyst was added thereto, followed by catalytic reduction for 20 hours at room temperature under hydrogen atmospheric pressure. The catalyst was filtered off, and then, the solvent was distilled off under reduced pressure. The residue was treated with hexane, whereupon the precipitate thereby obtained was collected by filtration and then dried to obtain the above-identified compound as colorless crystalline powder, mp 55-57°C.

12.97 g of the di-tert-butyl ester thus obtained and 13.24 g of cinchonidine was dissolved under heating in 1 liter of carbon tetrachloride. Then, seed crystals were added thereto, and the mixture was left to stand at room temperature for 24 hours. The crystals were collected by filtration and then again dissolved under heating in 1 liter of carbon tetrachloride, and seed crystals were added thereto, and the mixture was left to stand for 24 hours. This operation was further repeated twice to obtain a cinchonidine salt of the above-identified compound, which is named as the (S*)-isomer for the sake of convenience, $[\alpha]^{20}_D -62.7^\circ(c\ 1.0, \text{chloroform})$.

The cinchonidine salt thus obtained was dissolved in a mixed solution of ethyl ether and 1N hydrochloric acid under cooling with ice, and the organic layer was separated and then post-treated in accordance with a conventional method to obtain the (S*)-isomer of the above-identified compound as colorless oily substance, $[\alpha]^{20}_D +4.44^\circ(c\ 0.92, \text{chloroform})$.

The fraction containing a large amount of the other mirror image isomer obtained in the above optical resolution operation, was converted to a free acid, and then, the same operation was carried out in

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isopropyl ether using quinine, whereby the mirror image isomer named as the (R*)-isomer for the sake of convenience, was obtained.

EXAMPLE 3

5

Preparation of (2RS,3RS)-3-tert-butoxycarbonyl-5-
oxotetrahydrofuran-2-carboxylic acid

10

(1) Preparation of (2RS,3SR)-2-diphenylmethoxycarbonyl-5-
oxotetrahydrofuran-3-carboxylic acid

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262 mg of (2RS,3SR)-5-oxotetrahydrofuran-2,3-dicarboxylic acid was dissolved in 5 ml of acetone, and 291 mg of diphenyldiazomethane was added thereto, followed by stirring at room temperature for 20 minutes. The reaction solution was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 100/1 to 10/1) to obtain the above-identified compound as white powder.

20

(2) Preparation of 3-tert-butyl 2-diphenylmethyl (2RS,3RS)-5-
oxotetrahydrofuran-2,3-dicarboxylate

25

163 mg of (2RS,3SR)-2-diphenylmethoxycarbonyl-5-oxotetrahydrofuran-3-carboxylic acid, 59 mg of 4-dimethylaminopyridine and 36 mg of tert-butanol, were dissolved in 4 ml of methylene chloride, and 110 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added thereto, followed by stirring at room temperature for 13 hours. The reaction solution was diluted with methylene chloride, then sequentially washed with a 10% citric acid aqueous solution, a saturated sodium hydrogencarbonate aqueous solution and a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then, the solvent was distilled off under reduced pressure. The residue was purified by silica

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gel column chromatography (hexane/ethyl acetate = 10/1) to obtain the above-identified compound as colorless oily substance.

5 (3) Preparation of (2RS,3RS)-3-tert-butoxycarbonyl-5-
oxotetrahydrofuran-2-carboxylic acid

148 mg of 3-tert-butyl 2-diphenylmethyl (2RS,3RS)-5-oxotetrahydrofuran-2,3-dicarboxylate was dissolved in 4 ml of ethyl acetate, and 15 mg of a 10% palladium-carbon catalyst was added thereto, followed by catalytic reduction for 15 hours at room
10 temperature under hydrogen atmospheric pressure. The catalyst was filtered off, and then, the solvent was distilled off under reduced pressure. The residue was washed with benzene to obtain the above-identified compound as white crystalline powder.

15 EXAMPLE 4

Preparation of (2R*)-2-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic
20 acid and (2R*)-2-[N-{(1RS,2RS,4Z)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

(1) Preparation of di-tert-butyl (2R*)-2-[N-{(1RS,2RS)-4,4-diethoxy-1-methyl-2-(3,4-methylenedioxyphenyl)butyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinate
25 436 mg of N-{(1RS,2RS)-4,4-diethoxy-1-methyl-2-(3,4-methylenedioxyphenyl)butyl}-2-naphthylmethylamine obtained in a manner similar to Example 1, 346 mg of 1,2-di-tert-butyl
30 (R*)-1,2,3-propanetricarboxylate obtained in Example 2 and 122 mg of 4-dimethylaminopyridine, were dissolved in 5 ml of methylene chloride, and 249 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added thereto, followed by stirring at room temperature for 14 hours. The reaction solution was diluted with ethyl

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acetate, then, sequentially washed with 1N hydrochloric acid, saturated sodium hydrogen carbonate aqueous solution and a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1 to 5/1) to obtain the above-identified compound as a colorless foam.

(2) Preparation of di-tert-butyl (2R*)-2-[N-{(1RS,2RS)-3-formyl-1-methyl-2-(3,4-methylenedioxyphenyl)propyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinate

636 mg of di-tert-butyl (2R*)-2-[N-{(1RS,2RS)-4,4-diethoxy-1-methyl-2-(3,4-methylenedioxyphenyl)butyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinate was dissolved in 12 ml of tetrahydrofuran, and 3 ml of 2N hydrochloric acid was added thereto, followed by stirring at room temperature for 3 hours. To the reaction solution, a saturated sodium hydrogencarbonate aqueous solution was added, and the mixture was extracted with ethyl acetate. Then, the organic layer was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then, the solvent was distilled off under reduced pressure to obtain the above-identified compound as colorless oily substance.

(3) Preparation of di-tert-butyl (2R*)-2-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinate

53 mg of 60% oily sodium hydride was suspended in 5 ml of tetrahydrofuran, and 634 mg of 2-benzoxazolylmethyltriphenylphosphonium bromide was added thereto, followed by stirring at room temperature for 30 minutes. 5 ml of a tetrahydrofuran solution containing 563 mg of di-tert-butyl (2R*)-2-[N-{(1RS,2RS)-3-formyl-1-methyl-2-(3,4-methylenedioxyphenyl)propyl}-N-(2-

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naphthylmethyl)carbamoylmethyl]succinate was added thereto, followed by stirring at room temperature for 12 hours. Then, water was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then, the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate = 10/1 to 5/1) to obtain the above-identified E isomer compound and Z-isomer of the above-identified compound, respectively, as a colorless foam.

(4) Preparation of (2R*)-2-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

486 mg of di-tert-butyl (2R*)-2-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinate was dissolved in 10 ml of formic acid, followed by stirring at room temperature for 12 hours. Then, formic acid was distilled off under reduced pressure to obtain the above-identified compound as white solid.

¹H-NMR(CDC1₃) δ;0.91-1.00(3H, m), 2.30-3.70(8H, m), 4.20-5.30(3H, m), 5.90-5.94(2H, m), 6.43(1H, d, J=15.7Hz), 6.57-6.76(4H, m), 7.26-7.84(11H, m) FAB-MS:635(M+H)

By the same treatment as above except that di-tert-butyl (2R*)-2-[N-{(1RS,2RS,4Z)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinate was used, Z-isomer of the above-identified compound was obtained.

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EXAMPLE 5

Preparation of disodium (3RS,4RS)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxy-4-hydroxybutanoate

- (1) Preparation of (2RS,3RS)-2-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-5-oxotetrahydrofuran-3-carboxylic acid.
- 47 mg of tert-butyl (2RS,3RS)-2-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl) carbamoyl]-5-oxotetrahydrofuran-3-carboxylate prepared in a manner similar to Example 4 except that (2RS,3RS)-3-tertbutoxycarbonyl-5-oxotetrahydrofuran-2-carboxylic acid obtained in Example 3 was used, instead of the 1,2-di-tert-butyl (R*)-1,2,3,-propanetricarboxylate in Example 4, was dissolved in 1 ml of formic acid, and the solution was left to stand at room temperature overnight. The reaction solution was distilled under reduced pressure. Then, toluene was added to the residue, followed by distillation again. The product was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1 to chloroform/methanol = 50/1) to obtain the above-identified compound as white solid.

¹H-NMR(CDC13)δ:0.99 and 1.10(total 3H, each d, J=6.2Hz, 6.3Hz), 2.50-3.10(5H, m), 4.15-4.25 and 4.37-4.47(total 1H, each m), 4.50-5.35(4H, m), 5.73, 5.75, 5.88 and 5.94(total 2H, each s), 6.07 and 6.36(total 1H, each d, each J=15.8Hz), 6.60-6.75(4H, m), 7.25-7.82(11H, m)

FAB-MS:633(M+H)

- (2) Disodium (3RS,4RS)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxy-4-hydroxybutanoate

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8 mg of the lactone thus obtained was dissolved in a mixed solution of 1 ml of methanol and 1 ml of tetrahydrofuran, and 26 μ l of a 1N sodium hydroxide aqueous solution was added under cooling with ice with stirring, followed by stirring at room temperature for 10 minutes. The reaction solution was evaporated to dryness under reduced pressure to obtain the above-identified compound as white solid.

$^1\text{H-NMR}(\text{CDCl}_3)\delta$: 0.91 and 1.03 (total 3H, each d, $J=6.0\text{Hz}$ and 6.7Hz), 2.35-3.40 (6H, m), 4.60-5.10 (4H, m), 5.86 and 5.90 (total 2H, each s), 5.90-6.95 (5H, m), 7.28-8.01 (11H, m)

FAN-MS: 695 (M+H)

EXAMPLE 6

Preparation of disodium (3S, 4S)-4-[N-{1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxy-4-hydroxybutanoate (Compound D)

(1) Preparation of N-[(1R,2R)-4,4-diethoxy-1-methyl-2-(3,4-methylenedioxyphenyl)butyl]-2-naphthylmethylamine

(1-1) Preparation of 5,5-diethoxy-3-(3,4-methylenedioxyphenyl)pentan-2-one

11.7 g of (3,4-methylenedioxyphenyl)acetone was dissolved in 100 ml of dimethylformamide, and 2.76 g of 60% oily sodium hydride and 20.9 g of 2,2-diethoxyethyl iodide was added under cooling with ice with stirring, followed by stirring at room temperature for 2 hours. The reaction solution was poured into 100 ml of water and extracted with diethyl ether. Then, the organic layer was washed with a saturated sodium chloride aqueous solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The residue

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was purified by silica gel column chromatography (hexane/ethyl acetate = 15/1 to 10/1) to obtain the above-identified compound.

(1-2) Preparation of (2RS,3SR)-5,5-diethoxy-3-(3,4-methylenedioxyphenyl)pentan-2-ol

5 18.3 g of (3,4-methylenedioxyphenyl)acetone was dissolved in 200 ml of tetrahydrofuran, and 65 ml of a 1.0 M tetrahydrofuran solution of lithium tri-sec-butyl borohydride was added at -78°C under cooling with stirring, followed by stirring at the same temperature for 2
10 hours. To the reaction solution, 130 ml of a 1N sodium hydroxide aqueous solution was added under cooling with stirring, and then 150 ml of a 30% hydrogen peroxide aqueous solution was gradually dropwise added, followed by stirring at room temperature of one hour. The reaction solution was extracted by an addition of ethyl ether and water.
15 The organic layer was washed with a saturated sodium chloride aqueous solution and a saturated sodium thiosulfate aqueous solution and water then dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The residue was purified by silica gel column
20 chromatography (hexane/ethyl acetate = 15/1 to 10/1 to 3/1) to obtain the above-identified compound.

(1-3) Preparation of (2S,3R)-5,5-diethoxy-3-(3,4-methylenedioxyphenyl)pentan-2-ol

25 31.98 g of (2RS,3SR)-5,5-diethoxy-3-(3,4-methylenedioxyphenyl)pentan-2-ol was dissolved in 320 ml of vinyl acetate, and 15.1 ml of triethylamine was added thereto. Then 1.0 g of immobilized lipase (Toyothium LIP) was added thereto, followed by stirring at 30°C for 16 hours. Further, 0.9 g of immobilized lipase was added thereto,
30 followed by stirring at the same temperature for 46 hours. Then, insoluble matters were filtered off. The filtrate was diluted with ethyl acetate, then sequentially washed with 1N hydrochloric acid, a saturated sodium hydrogencarbonate aqueous solution and a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate.

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The drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate - 5/1 to 1/1) to obtain the above-identified compound, $[\alpha]_{D20}^{20} -31.8^\circ$ (c 1.0, methanol) as colorless oily substance and (2R,3S)-2-acetoxy-5,5-diethoxy-3-(3,4-methylenedioxyphenyl)pentane as colorless oily substance. Further, the absolute configuration of the above-identified compound was detered by Mosher method (J. Am. Chem. Soc., Vol. 113, p. 4092 (1991)).

- 10 (1-4) Preparation of (1R,2R)-4,4-diethoxy-1-methyl-2-(3,4-methylenedioxyphenyl)butylamine
-
- 4.19 g of (2S,3R)-5,5-diethyl-3-(3,4-methylenedioxyphenyl)pentan-2-ol was dissolved in 45 ml of ethyl acetate, and 1.64 ml of methanesulfonylchloride and 3.93 ml of triethylamine were added under cooling with ice thereto, followed by stirring under cooling with ice for 30 minutes. To the reaction solution, 50 ml of a saturated sodium hydrogen carbonate solution was added, followed by stirring at room temperature for 45 minutes. The reaction solution was extracted by an addition of ethyl acetate and water. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. the drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The residue was dissolved in 40 ml of dimethylformamide, and 4.58 g of sodium azide was added thereto, followed by stirring at 120°C for 30 minutes. The reaction solution was a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The residue was dissolved in a mixed solution of 40 ml of tetrahydrofuran, and 4 ml of water was added, followed by stirring at 90°C for 4.5 hours. The reaction solution was distilled under reduced pressure. Then, the residue was purified by silica gel column chromatography (ethyl acetate/methanol = 9/1) to obtain the above-identified compound.

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(1-5) Preparation of N-{(1R,2R)-4,4-diethoxy-1-methyl-2-(3,4-methylene-dioxyphenyl)butyl}-2-naphtylmethylamine

150 mg of (1R,2R)-4,4-diethoxy-1-methyl-2-(3,4-methylene-dioxyphenyl)butyl}-2-naphtylmethylamine was dissolved in 2
5 ml of methanol, and 79 mg of naphthoaldehyde was added thereto, followed by stirring at 60°C for 2 hours. To the reaction solution, 28 mg of sodium borohydride was added under cooling with ice thereto, followed by stirring under cooling with ice for 2 hours. The reaction solution was extracted by an addition of ethyl ether and water. The
10 organic layer was washed with a saturated sodium chloride aqueous solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 3/1) to obtain the above-identified compound.

15

(2) Preparation of (2S,3S)-3-tert-butoxycarbonyl-5-oxotetrahydrofuran-2-carboxylic acid

20 (2-1) Preparation of 3-tert-butyl 1,2-diethyl(1S,2R)-1-hydroxy-1,2,3-propanetricarboxylate

31 ml of a 1.69 M hexane solution of n-butyl lithium was dissolved in 30 ml of tetrahydrofuran, and 7.1 ml of diisopropylamine was added under cooling with ice, followed by stirring at the same temperature for 30 minutes. Then the mixture
25 was cooled to -78°C. 20 ml of a tetrahydrofuran solution containing 4.94 g of diethyl (S)-malate was dropwise added at a temperature of not higher than -50°C, followed by stirring at -20°C for 1.5 hours. The reaction solution was cooled to -78°C, and 20 ml of a tetrahydrofuran solution containing 5.58 g of tert-butyl promoacetate
30 and 4.66 g of hexamethylphosphoric triamide was dropwise added thereto at a temperature of not higher than -50°C, followed by stirring at room temperature for one hour. The reaction solution was poured into 150 ml of 0.5 N hydrochloric acid and extracted with diethyl ether. Then the organic layer was washed with a

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5 saturated sodium hydrogencarbonate aqueous solution and a saturated sodium chloride aqueous solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 4/1) to obtain the above-identified compound as yellow oily substance.

10 (2-2) Preparation of (2S,3R)-5-oxotetrahydrofuran-2,3-dicarboxylic acid
16.49 g of 3-tert-butyl 1,2-diethyl (1S,2R)-1-hydroxy-1,2,3-propanetricarboxylate, 100 ml of acetic acid and 50 ml of concentrated hydrochloric acid were mixed and stirred at 70°C for 12 hours. Acetic acid and hydrochloric acid were distilled off under reduced pressure. Then the residue was again dissolved in 100 ml of acetic acid and 50 ml of concentrated hydrochloric acid and stirred at 70°C for 12 hours. Acetic acid and hydrochloric acid were distilled off under reduced pressure. Then 100 ml of trifluoroacetic acid was added to the residue, followed by stirring at 60°C for 5 hours. Trifluoroacetic acid was distilled off under reduced pressure, and the residue was distilled off under reduced pressure, and the residue was crystallized from hexane-ethyl acetate to obtain the above-identified compound as white powder.

25 (2-3) Preparation of (2S,3R)-2-benzyloxycarbonyl-5-oxotetrahydrofuran-3-carboxylic acid
5.2 of (2S,3R)-5-oxotetrahydrofuran-2,3-dicarboxylic acid was dissolved in 88 ml of acetone, and 6.5 g of 1,1'-dicyclohexylcarbodiimide was added thereto, followed by stirring at room temperature for 2 hours. 3.26 ml of benzyl alcohol was added to the reaction solution, and stirred at the same temperature for 12 hours. Insoluble matters were filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate - 4/1 to

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chloroform:methanol - 50/1) to obtain the above-identified compound as yellow solid.

5 (2-4) Preparation of 2-benzyl 3-tert-butyl (2S,3S)-5-
oxotetrahydrofuran-2,3-dicarboxylate
7.93 g of (2S-3R)-2-benzoyloxycarbonyl-5-oxotetrahydrofuran-3-carboxylic acid was dissolved in 75 ml of chloroform, and 5.5 g of 4-dimethylaminopyridine, 8.6 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 5.7
10 ml of tert-butyl alcohol were sequentially added thereto, followed by stirring at room temperature for 60 hours. The reaction solution was poured into 1N hydrochloric acid cooled with ice, and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then the
15 solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1) to obtain the above-identified compound as white solid.

20 (2-5) Preparation of (2S,3S)-3-tert-butoxycarbonyl-5-
oxotetrahydrofuran-2-carboxylic acid
6.4 g of 2 benzyl 3-tert-butyl (2S,3S)-5-oxotetrahydrofuran-2,3-dicarboxylate was dissolved in 80 ml of ethyl acetate, and 640 mg of a 10% palladium-carbon catalyst was added thereto, followed by catalytic reduction for 3 hours at room
25 temperature under hydrogen atmospheric pressure. The catalyst was filtered off, and the filtrate was evaporated to dryness under reduced pressure to obtain the above-identified compound as white solid.

30 (3) Preparation of ter-butyl (2S,3S)-2-[N-{1R,2R)-4,4-diethoxy-1-methyl-2-(3,4-methylenedioxyphenyl)butyl}-N-(2-naphtylmethyl)carbonyl]-5-oxotetrahydrofuran-3-
carboxylate
61 mg of N-((1R,2R)-4,4-diethoxy-1-methyl-2-(3,4-methylenedioxyphenyl)butyl)-2-naphtylmethylamine, 35 mg of

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(2S,3S)-3-tert-butoxycarbonyl-5-oxotetrahydrofuran-2-carboxylic acid and 83 μ l of triethylamine, were dissolved in 2 ml of chloroform, and 0.5 ml of a chloroform solution containing 34 mg of 2-chloro-1,3-dimethylimidazolinium chloride was added thereto
5 under cooling with ice followed by stirring at the same temperature of 30 minutes. The reaction solution was poured into water and extracted with ethyl acetate. The extract solution was dried over anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was distilled off under reduced pressure. The residue
10 was purified by silica gel column chromatography (hexane/ethyl acetate = 1/3) to obtain of the above-identified compound as colorless oily substance.

(4) Preparation of tert-butyl (2S,3S)-2-[N-{(1R,2R)-3-formyl-1-methyl-2-(3,4-methylenedioxyphenyl)propyl}-N-(2-naphtylmethyl)carbamoyl]-5-oxotetrahydrofuran-3-
15 carboxylate

490 mg of tert-butyl (2S,3S)-2-[N-{1R,2R)-4,4-diethoxy-1-methyl-2-(3,4-methylenedioxyphenyl)butyl}-N-(2-naphtylmethyl)carbamoyl]-5-oxotetrahydrofuran-3-carboxylate was
20 dissolved in 15 ml of tetrahydrofuran, and 5 ml of 1 N hydrochloric acid was added thereto, followed by stirring at room temperature for 24 hours. To the reaction solution, a saturated sodium hydrogencarbonate aqueous solution was added, and the mixture was
25 extracted with ethyl acetate. Then the organic layer was washed with a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The residue was
30 purified by silica gel column chromatography (Hexane/ethyl acetate = 5/1) to obtain the above-identified compound as colorless oily substance.

(5) Preparation of tert-butyl (2S,3S)-2-[N-{(1R,2R4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-

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pentenyl}-N-(2-naphthylmethyl)carbamoyl]-5-
oxotetrahydrofuran-3-carboxylate.

- 29 mg of 60% oily sodium hydride was suspended in 15 ml of tetrahydrofuran, and 389 mg of 2-benzoxazolylmethyl(triphenyl)phosphonium bromide was added thereto, followed by stirring at room temperature for 2 hours. 5 ml of a tetrahydrofuran solution containing 319 mg of tert-butyl (2S,3S)-2-[N-{(1R,2R)-3-formyl-1-methyl-2-(3,4-methylenedioxyphenyl)propyl}-N-(2-naphthylmethyl)carbamonyl]-5-oxotetrahydrofuran-3-carboxylate was added thereto, followed by stirring at room temperature overnight. Then water was added to the solution, and the mixture was extracted with diethyl ether. The organic layer was washed with a saturated sodium chloride aqueous solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate - 3/1) to obtain the above-identified compound as a colorless foam.
- (6) Preparation of (2S,3S)-2-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-5-oxotetrahydrofuran-3-carboxylic acid.
- 295 mg of tert-butyl (2S,3S)-2-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-5-oxotetrahydrofuran-3-carboxylate was dissolved in 5 ml of formic acid, and the solution was left to stand at room temperature overnight. The reaction solution was distilled under reduced pressure. The product was purified by silica gel column chromatography (chloroform/methanol - 50/1) to obtain the above-identified compound as white solid.
- ¹H-NMR(CDCl₃)δ:0.99 and 1.10 (total 3H, each d, J=6.2 Hz, 6.3 Hz), 2.50-3.10 (5H, m), 4.15-4.25 and 4.37-4.47 (total 1H, each m), 4.50-5.35 (4H, m) 5.73, 5.75, 5.88 and 5.94 (total 2H, each s), 6.07 and 6.36

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(total 1H, each d, each J-15.8Hz), 6.60-6.75 (4H, m), 7.25-7.82 (11H, m) FAB-MS:633 (M+H)

- 5 (7) Preparation of disodium (2S,3S)-2-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxy-4-hydroxybutanoate

262 mg of the lactone thus obtained was dissolved in a mixed solution of 10 of methanol and 5 ml of water, and 0.91 ml of a 1N sodium hydroxide aqueous solution was added under cooling with ice with stirring, followed by stirring at room temperature overnight. The reaction solution was evaporated to dryness under reduced pressure. The residue was crystalized from 2 ml of methanol and 10 ml of diethyl ether to obtain the above-identified compound as white solid.

15 ¹H-NMR(CD₃OD)δ:0.83-1.08 (3H, m), 2.30-3.20 (6H, m), 4.53-5.10(4H, m), 5.85 and 5.89 (total 2H, each s), 5.80-6.95 (4H, m), 7.20-8.06 (12H, m)
FAB-MS:695(M+H)

20

EXAMPLE 7

Preparation of sodium 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)-carbamoyl]-3-tert-butoxycarbonyl-4-hydroxy-3-butenate (Compound C)

- 25 (1) Preparation of methyl (3S,4S)-4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxybutanoate

193 mg of tert-butyl (2S,3S)-2-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-5-oxotetrahydrofuran-3-carboxylate was

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- dissolved in a mixed solution of 5 ml of tetrahydrofuran and 2 ml of water, and 0.31 ml of a 1N sodium hydroxide aqueous solution was added thereto, followed by stirring at room temperature for 15 hours. The reaction solution was acidified (about pH4) by an addition of 1N hydrochloric acid and then extracted with ethyl acetate. The extract solution was dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The obtained carboxylic acid was dissolved in ethyl acetate, and a slightly excess amount of diazomethane was added at room temperature. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate - 2/1) to obtain the above-identified compound as colorless oily substance.
- 15 (2) Preparation of methyl 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxy-3-butenate
- 20 36 mg of methyl (3S,4S)-4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxybutanoate was dissolved in 2 ml of chloroform, and 42 mg of a Dess-Martin reagent (periodenane) was added thereto, followed by stirring at room temperature for 1 hour. The reaction solution was
- 25 poured into a mixed solution of a saturated sodium hydrogencarbonate aqueous solution and a saturated sodium thiosulfate aqueous solution and extracted with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then the
- 30 solvent was distilled off under reduced pressure. The residue was purified by silica gel thin layer chromatography (Kieselgel™ 60F254, Art™ 5744; hexane/ethyl acetate - 3/2) to obtain the above-identified compound as colorless oily substance.

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(3) Preparation of 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxy-3-butenic acid

5 9.9 mg of methyl 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxy-3-butenate was dissolved in a mixed solution of 3 ml of tetrahydrofuran and 1 ml of water, and 140 μ l of a 1N sodium
10 hydroxide aqueous solution was added thereto, followed by stirring at room temperature for 4 hours. The reaction solution was acidified by an addition of 1N hydrochloric acid and extracted with ethyl acetate. The extract solution was dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then the
15 solvent was distilled off under reduced pressure. The residue was purified by silica gel thin layer chromatography (KieselgelTM 60F254' ArtTM 5744; chloroform/methanol = 10/1) to obtain the above-identified compound as a colorless foam.
¹H-NMR(CDCl₃) δ : 0.96-1.06 (3H, M), 1.41-1.51 (9H, m), 2.30-3.29
20 (5H, m), 4.15-4.98 (4H, m), 5.88-6.34 (3H, m), 6.41-6.74 (4H, m), 7.21-7.88 (11H, m)
FAB-MS: 705(M+H)

(3) Preparation of sodium 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxy-3-butenate

25 850 mg of 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxy-3-butenic acid, prepared as described in Step (3), was dissolved in 25 ml of methanol, and sodium methoxide was added thereto. The
30 solvent was distilled off under reduced pressure. The residue was

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solidified from ether and hexane to obtain the above-identified compound as a white powder.

¹H-NMR(CD₃OD) δ:0.99-1.10 (3H, m), 1.45-1.53 (9H, m), 2.16-3.53 (5H, m), 4.19-5.22 (4H, m), 5.50-6.33 (3H, m), 6.37-6.86 (4H, m), 7.22-8.15 (11H, m)

FAB-MS:727(M+Na)

EXAMPLE 8

- 10 Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone and 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyloxy-3-phenyl-propionyl-homoserine

- 15 Step A: Preparation of N-(α-chloroacetyl)-L-isoleucinol

To a stirred solution of L-isoleucinol (20 g, 0.17 mol) and triethylamine (28.56 ml, 0.204 mol) in CH₂Cl₂ (500 ml) at -78°C was added chloroacetyl chloride (16.3 ml, 0.204 mol) over 5 minutes. The cooling bath was removed and the solution allowed to warm to -20°C. The mixture was diluted with EtOAc and washed sequentially with 1 M HCl, and brine and dried (Na₂SO₄). Evaporation in vacuo afforded the amide title compound (35 g, 100%).

R_f = 0.3 CH₂Cl₂: MeOH (95:5);

- 25 ¹H NMR (CDCl₃) δ 6.80 (1H, brd, J = 5 Hz), 4.10 (2H, s), 3.84 (1H, m), 3.79 (2H, m), 2.65 (1H, brs), 1.72 (1H, m), 1.55 (1H, m), 1.17 (1H, m), 0.96 (3H, d, J = 6Hz) 0.90 (3H, t, J=6 Hz).

- Step B: Preparation of 5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one

- 30 To a stirred solution of N-(α-chloroacetyl)-L-isoleucinol (7.4 g, 0.038 mol) in THF (125 ml) under argon at 0°C was slowly added sodium hydride (2.2 g of a 60% dispersion in mineral oil, 0.055 mol) with concomitant gas evolution. After completing the addition, the mixture was warmed to room temperature (R.T.) and

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stirred for 16 hr. Water (2.8 ml) was added and the solvents evaporated in vacuo. The residue was dissolved in CHCl₃ (70 ml) and washed with water saturated NaCl solution. The organic layer was dried (Na₂SO₄) and evaporated in vacuo. The residue was

5 chromatographed using silica gel eluting with CH₂Cl₂:MeOH (96:4) to afford the lactam title compound (4.35 g, 72%) as a white solid. R_f = 0.35 CH₂Cl₂:MeOH (95:5);

¹H NMR δ (CDCl₃) 6.72 (1H, brs), 4.20 (1H, d, J = 14.5 Hz), 4.10 (1H, d, J = 14.5 Hz), 3.88 (1H, dd, J = 9 and 3.5 Hz), 3.58 (1H, dd, J = 9 and 6.5 Hz), 3.45 (1H, brqt, J = 3.5 Hz), 1.70-1.45 (2H, m), 1.34

10 - 1.15 (1H, m), 0.96 (3H, t, J = 6.5 Hz), 0.94 (3H, d, J = 6.5 Hz).

Step C: Preparation of N-(tert-butoxycarbonyl)-5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one

15 5(S)-[1(S)-Methyl]propyl-2,3,5,6-tetrahydro 4H-1,4-oxazin-3-one (12.2 g, 0.0776 mol) and DMAP (18.9 g, 0.155 mol) were dissolved in methylene chloride (120 ml) under argon at R.T. Boc anhydride (33.9 g, 0.155 mol) was added to the stirred solution in one portion, with concomitant gas evolution and the mixture was

20 stirred at R.T. for 16 hr. The solvent was evaporated in vacuo and the residue was taken up in ethyl acetate and washed sequentially with 10% citric acid, 50% NaHCO₃ and finally brine. The organic extract was dried (Na₂SO₄) and evaporated in vacuo. Chromatography of the residue over silica gel eluting with 20% EtOAc in hexanes

25 afforded the title compound as a white solid. R_f = 0.75 EtOAc:hexanes (20:80); mp 59-60°C

Anal. Calc'd. for C₁₃H₂₃O₄N : C, 60.68; H, 9.01; N, 5.44. Found: C, 60.75; H, 9.01; N, 5.58.

¹H NMR (CDCl₃) δ 4.25 (1H, d, J = 15 Hz), 4.15 (1H, d, J = 15 Hz),

30 4.15 - 4.00 (2H, m), 3.73 (1H, dd, J = 10 and 2 Hz), 1.88 (1H, qt, J = 6 Hz), 1.55 (9H, s), 1.50 - 1.36 (1H, m), 1.35 - 1.19 (1H, m) 1.00 (3H, d, J = 6 Hz) 0.95 (3H, d, J = 6.5 Hz).

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Step D: Preparation of N-(tert-Butoxycarbonyl)-2(S)-benzyl-5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one

A solution of N-(tert-butoxycarbonyl)-5(S)-[1(S)-methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one (5.75 g, 22.34 mmol) in DME (100 ml) under argon was cooled to -60°C. The cold solution was transferred via canula to a second flask containing sodium bis(trimethylsilyl)amide (24.58 ml of a 1M solution in THF, 24.58 mmol) at -78°C under argon. After stirring for 10 minutes, benzyl bromide (2.25 ml, 18.99 mmol) was added over 5 minutes and the resulting mixture was stirred at -78°C for 3 hours. After this time, the reaction mixture was transferred via cannula to another flask containing sodium bis(trimethylsilyl)amide (24.58 ml of a 1M solution in THF, 24.58 mmol) at -78°C, under argon. After stirring for a further 5 minutes, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (24.6 ml) and allowed to warm to room temperature. This mixture was diluted with brine (50 ml) and water (20 ml) and then extracted with ethyl acetate (2 x 100 ml). The organic extracts were washed with brine (50 ml) and evaporated in vacuo to afford an oil. Chromatography of the residue over silica gel (230-400 mesh, 300 g) eluting with 10-20% ethyl acetate in hexanes afforded the title compound as a clear oil.

Rf = 0.25 EtOAc:Hexanes (20:80);
¹H NMR (CDCl₃) δ 7.35 - 7.15 (5H, m), 4.31 (1H, dd, J = 6 and 2 Hz), 4.03 (1H, d, J = 12 Hz), 3.88 (1H, dd, J = 6 and 1 Hz), 3.66 (1H, dd, J = 12 and 2 Hz), 3.29 (1H, dd, J = 12 and 3 Hz), 1.54 (9H, s), 3.12 (1H, dd, J = 12 and 7 Hz), 1.47 (1H, m), 1.25 (1H, m), 1.10 (1H, m), 0.83 (3H, d, J = 6 Hz), 0.80 (3H, t, J = 6 Hz).

30 Step E: Preparation of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]pentyloxy-3-phenyl-propionic acid

To a stirred solution of N-(tert-butoxycarbonyl)-2(S)-benzyl-5(S)-[1(S)-methyl]-propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one (5.1 g, 14.7 mmol) in THF (150 ml) and water (50 ml) at 0°C

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was added hydrogen peroxide (15 ml of a 30% aqueous solution, 132 mmol) and lithium hydroxide (3.0 g, 63.9 mmol). After stirring for 30 minutes, the reaction was quenched with a solution of sodium sulfite (28.25 g, 0.224 mol) in water (70 ml). The THF was

5 evaporated in vacuo and the aqueous phase was acidified to pH 3-4 by addition of 10% citric acid solution and extracted with EtOAc. The organic extracts were dried (Na₂SO₄), evaporated in vacuo and the residue purified by chromatography over silica gel eluting with 4% MeOH in CH₂Cl₂ to give the lactam 2(S)-benzyl-5(S)-[1(S)-

10 methyl]propyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-3-one and then with 20% MeOH in CH₂Cl₂ to afford the title compound (4.03 g, 75%) as a viscous oil.

R_f = 0.4 MeOH:CH₂Cl₂ (5:95) + 0.3% AcOH;

¹H NMR (d₆ DMSO) δ 7.35 - 7.10 (5H, m), 6.68 (1H, br, s), 3.75

15 (1H, dd, J = 7.5 and 2.5 Hz) 3.54 (1H, m), 3.5 - 3.2 (2H, m) 2.99 (1H, dd, J = 12.5 and 2.5 Hz), 2.75 (1H, dd, J = 12.5 and 7.5 Hz), 1.50 - 1.35 (11H, m), 0.98 (1H, sept, J = 6 Hz), 0.78 (3H, t, J = 6 Hz), 0.65 (3H, d, J = 6 Hz);

FAB MS 366 (MH⁺) 266 (MH₂⁺ - CO₂^tBu).

20

Step F: Preparation of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]-pentyloxy-3-phenyl-propionyl-homoserine lactone

To a stirred solution of N-(tert-butoxycarbonyl)-2(S)-

25 [2(S)-amino-3(S)-methyl]-pentyloxy-3-phenylpropionic acid (0.53 g, 1.45 mmol) and 3-hydroxy-1,2,3,-benzotriazin-4(3H)-one (HOOBT) (0.26 g, 1.6 mmol) in DMF (15 ml) at room temperature was added EDC (0.307 g, 1.6 mmol) and L-homoserine lactone hydrochloride (0.219 g, 6.0 mmol). The pH was adjusted to pH= 6.5 by addition of

30 NEt₃ (the pH was monitored by application of an aliquot of the reaction mixture to a moist strip of pH paper). After stirring at room temperature for 16 hr, the reaction was diluted with EtOAc and washed with saturated NaHCO₃ and then brine and dried (NaSO₄). Evaporation in vacuo (sufficient to remove DMF) and

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chromatography over silica gel eluting with 5% acetone in CH₂Cl₂ afforded the title compound as a white solid, mp 115-117°C.

R_f = 0.3 Acetone: CH₂Cl₂ (5:95).

¹H NMR (CDCl₃) δ 7.73 (1H, brd, J=5 Hz), 7.40-7.15 (5H, m), 4.68 (1H, dt, J=9 and 7.5 Hz), 4.65-4.35 (2H, m), 4.33-4.18 (1H, m), 4.20 (1H, dd, J=7 and 3 Hz), 3.78 (1H, m), 3.49 (1H, dd, J=7.5 and 4.0 Hz), 3.37 (1H, dd, J=7.5 and 6.5 Hz), 3.15 (1H, dd, J=11.5 and 2 Hz), 2.86 (1H, dd, J=11.5 and 7.5 Hz), 2.68 (1H, m), 2.11 (1H, q, J=9 Hz), 1.55-1.30 (11H, m), 1.07 (1H, m), 0.87 (3H, t, J=6.3 Hz), 0.79 (3H, d, J=6 Hz).

Step G: Preparation of 2(S)-[2(S)-amino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-homoserine lactone hydrochloride

Anhydrous HCl gas was bubbled through a cold (0°C) solution of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine lactone (3.0 g, 6.7 mmol) in ethyl acetate (120 ml) until a saturated solution was obtained. The resulting mixture was stirred at 0°C for 1 hr. The solution was purged with nitrogen and the mixture concentrated in vacuo to afford the title compound as a sticky foam which was used without further purification.

¹H NMR (d₆ DMSO) δ 8.60 (1H, d, J=7 Hz), 8.08 (3H, brs), 7.35-7.15 (5H, m), 4.60 (1H, qt, J=8 Hz), 4.36 (1H, t J=7.5 Hz), 4.22 (1H, q, J=7.5 Hz), 4.15-3.95 (2H, m), 3.64 (1H, dd, J=9 and 2.5 Hz), 3.15-3.00 (2H, m), 2.92 (1H, dd, J=12.5 and 5.0 Hz), 2.40-2.15 (2H, m), 1.65 (1H, m), 1.43 (1H, m), 1.07 (1H, m), 0.82 (3H, t, J=6 Hz), 0.72 (3H, d, J=6.0 Hz).

Step H: Preparation of 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)-amino-3-triphenylmethylmercap-to]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-homoserine lactone

2(S)-[2(S)-Amino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine hydrochloride (6.7 mmol) and N-(tert-butoxy-

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- carbonyl)-S-triphenylmethylcysteine aldehyde (0.74 g, 7.5 mmol) (prepared from N-(tert-butoxycarbonyl)-S-triphenylmethylcysteine by the procedure of Goel, O.P.; Krolls, U.; Stier, M.; Keston, S. Org. Syn. 1988, 67, 69.) and potassium acetate (3.66 g, 8.2 mmol) were dissolved in methanol (48 ml). Activated 4A molecular sieves (6g) and then Na(CN)BH₃ (0.70 g, 10.7 mmol) were added and the resulting slurry was stirred under argon at room temperature for 16 hr. The solids were removed by filtration and the filtrate evaporated in vacuo. The residue was dissolved in EtOAc and washed sequentially with saturated aqueous NaHCO₃ and brine and then dried (Na₂SO₄). Evaporation in vacuo afforded an oil which was purified by chromatography over silica gel eluting with a gradient of 30-50% EtOAc in hexane to afford the title compound contaminated with a small amount of the corresponding methyl ester.
- ¹H NMR (CD₃OD) δ 7.60-7.05(20H, m), 4.64 (1H, d, J=9.0Hz), 4.39 (1H, br t, J=9Hz), 4.25(1H, m), 3.93 (1H, m), 3.75-3.60(1H, m), 3.55 (1H, dd, J=9.0 and 2Hz), 3.20 (1H, dd, J=9.0 and 6.0 Hz), 3.04 (1H, dd, J=15.0 and 5.0 Hz), 2.85 (1H, dd, J=15.0 and 9.0 Hz), 2.60 (1H, dd, J=12.0 and 5.0 Hz), 2.50-2.15 (7H, m), 1.45 (9H, s), 1.40-1.20 (1H, m), 1.07 (1H, m), 0.87 (3H, t, J=6 Hz), 0.67 (3H, d, J=6.0 Hz).

Step I: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentylloxy-3-phenylpropionyl-homoserine lactone

- To a stirred solution of 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]pentylloxy-3-phenylpropionyl-homoserine lactone (2.72 g, 3.49 mmol) in CH₂Cl₂ (90 ml) was added HSiEt₃ (2.16 ml, 13.5 mmol) and TFA (43.2 ml, 0.56 mol) and the solution was stirred at R.T. under argon for 2 hrs. The solvent was evaporated in vacuo and the residue partitioned between 0.1% aqueous TFA (200 ml) and hexanes (100 ml). The aqueous layer was separated and washed with hexanes (20 ml) and then lyophilised. The resulting white lyophilate was chromatographed in 5 equal portions over a Waters Prepak

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cartridge (C-18, 15-20 mM 100 Å) eluting with a gradient of 95:5 to 5:95 0.1% TFA in H₂O : 0.1% TFA in CH₃CN at 100 ml/min over 60 min. The desired compound eluted after 19 min. The CH₃CN was evaporated in vacuo and the aqueous solution lyophilised to afford the title compound (1.95 g, 77%) as the TFA salt.

The salt is hygroscopic and is prone to disulphide formation if left in solution and exposed to air.

¹H NMR δ (CD₃OD) 7.40-7.15 (5H, m), 4.55-5.40 (2H, m), 4.33 (1H, m), 4.18 (1H, m), 3.90-3.62 (3H, m), 3.53 (1H, dd, J=10.5 and 4.0 Hz), 3.37 (1H, dd, J=10.5 and 6.0 Hz), 3.23 (1H, m), 3.15-2.95 (2H, m), 2.88 (1H, dd, J=12.5 and 5.0 Hz), 2.55-2.25 (2H, m), 1.92 (1H, m), 1.49 (1H, m), 1.23 (1H, m), 0.94 (3H, t, J=6 Hz), 0.90 (3H, d, J=6Hz).

FAB MS 873 (2M-H⁺) 438 (MH⁺) 361 (MH⁺Ph)

Anal. calc'd for C₂₂H₃₆O₄N₃S 2.6 TFA:C, 43.58; H, 5.25; N, 5.82. Found: C, 43.62; H, 5.07; N, 5.80.

Step J: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyl-oxy-3-phenylpropionyl-homoserine

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propyl-amino-3(S)-methyl]pentyl-oxy-3-phenylpropionyl-homoserine lactone (0.00326 mmol) was dissolved in methanol (0.0506 ml) and 1N sodium hydroxide (0.0134 ml) was added followed by methanol (0.262 ml). The conversion of the lactone to the hydroxy-acid was confirmed by HPLC analysis and NMR.

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EXAMPLE 9

Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-
3(S)-methyl]pentylloxy-3-phenylpropionyl-methionine sulfone methyl
5 ester (Compound 5)

Step A: Preparation of Methionine sulfone methyl ester

Thionyl chloride (2.63 ml, 36 mmol) was added
dropwise to a stirred solution of N-Boc-Met sulfone (5 g, 18 mmol)
10 in methanol (40 ml) cooled at 0°C. After the completion of the
addition, the resulting mixture was warmed to room temperature and
stirred overnight. The reaction mixture was re-cooled to 0°C and
slowly treated with solid sodium bicarbonate to adjust the pH to 7.
The mixture was concentrated in vacuo to remove methanol and the
15 residue was dissolved in a minimum amount of water (solution pH ca.
10) and extracted with ethyl acetate four times. The combined
extracts were dried (Na₂SO₄) and concentrated to give the title
compound (1.5 g). NMR (CD₃OD) δ 2.04 (H, m), 2.21 (H, m), 2.98
(3H, s), 3.23 (2H, t, J=7Hz), 3.63 (H, d of d, J=8.6Hz), 3.77 (3H, s).

20

Step B: Preparation of N-(tert-Butoxycarbonyl)-2(S)-[2(S)-
amino-3(S)-methyl]-pentylloxy-3-phenyl-propionyl-
methionine sulfone methyl ester

The title compound was prepared in the same fashion as
25 that described in Example 8, Step F, but using methionine sulfone
methyl ester in place of homoserine lactone hydrochloride. NMR
(CD₃OD) δ 0.80 (3H, d, J=6Hz), 0.88 (3H, t, J=6Hz), 1.12 (H, m),
1.47 (9H, s), 2.10 (H, m), 2.32 (H, m), 2.93 (3H, s), 3.5~3.7 (2H, m),
3.74 (3H, s), 4.01 (H, d of d, J=7.4Hz), 4.60 (H, d of d, J=9.5Hz),
30 6.60 (H, d, J=8Hz), 7.25 (5H, m).

Step C: Preparation of 2(S)-[2(S)-Amino-3(S)-methyl]-
pentylloxy-3-phenylpropionyl-methionine sulfone methyl
ester hydrochloride

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The title compound was prepared in the same fashion as that described in Example 8, Step G, but using N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]pentyl-oxy-3-phenylpropionyl-methionine sulfone methyl ester in place of N-(tert-butoxycarbonyl)-2(S)-[2(S)-amino-3(S)-methyl]pentyl-oxy-3-phenylpropionyl-homoserine lactone. NMR (CD₃OD) δ 0.85 (3H, d, J=6Hz), 0.94 (3H, t, J=6Hz), 1.20 (H, m), 1.52 (H, m), 1.72 (H, m), 2.14 (H, m), 2.38 (H, m), 2.98 (3H, s), 3.57 (H, d of d, J=12, 6Hz), 3.73 (H, d of d, J=12, 9Hz), 3.78 (3H, s), 4.15 (H, d of d, J=8.6Hz), 4.63 (H, d of d, J=8.5Hz), 7.30 (5H, m).

Step D: Preparation of 2(S)-[2(S)-[2(R)-(tert-Butoxy-carbonyl)-amino-3-triphenylmethylmercapto]-propylamino-3(S)-methyl]pentyl-oxy-3-phenyl-propionyl-methionine sulfone methyl ester

The title compound was prepared in a similar fashion as that described in Example 8, Step H, but using 2(S)-[2(S)-amino-3(S)-methyl]pentyl-oxy-3-phenyl-propionyl-methionine sulfone methyl ester hydrochloride in place of 2(S)-[2(S)-amino-3(S)-methyl]pentyl-oxy-3-phenylpropionyl-homoserine lactone hydrochloride. NMR (CD₃OD) δ 0.70 (3H, d, J=6Hz), 0.88 (3H, t, J=6Hz), 1.10 (H, m), 1.47 (9H, s), 2.15 (H, m), 2.67 (H, m), 2.92 (3H, s), 3.67 (H, m), 4.68 (H, d of d, J=10, 6Hz), 7.15~7.45 (20H, m).

Step E: Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]pentyl-oxy-3-phenylpropionyl-methionine sulfone methyl ester

The title compound was prepared in a similar fashion as that described in Example 8, Step I, but using 2(S)-[2(S)-[2(R)-(tert-butoxycarbonyl)amino-3-triphenylmethylmercapto]propylamino-3(S)-methyl]-pentyl-oxy-3-phenylpropionyl-methionine sulfone methyl ester in place of 2(S)-[2(S)-[2(R)-(tert-butoxy-carbonyl)-amino-3-triphenyl-methylmercapto]propylamino-3(S)-methyl]pentyl-oxy-3-

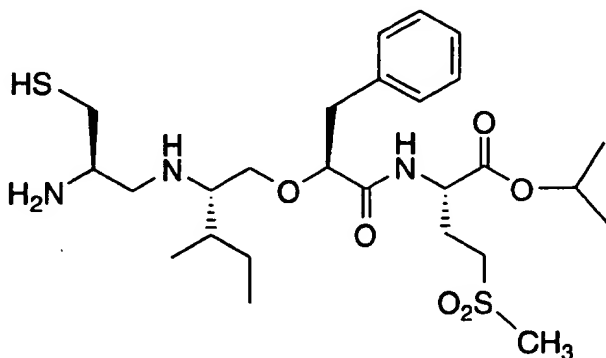
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phenyl-propionyl-homoserine lactone. NMR (CD₃OD) δ 0.83 (3H, d, J=6Hz), 0.93 (3H, t, J=6Hz), 1.20 (H, m), 1.51 (H, m), 1.80 (H, m), 2.22 (H, m), 2.43 (H, m), 3.00 (3H, s), 3.78 (3H, s), 4.20 (H, d of d, J=8.4Hz), 4.72 (H, d of d, J=10, 6Hz), 7.30 (5H, m).

5 FABMS m/z 532 (MH⁺).

EXAMPLE 10

10 Preparation of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A)



The title compound was prepared using methods A-E from Example 9, except for Method A. Methionine sulfone isopropyl ester was prepared by coupling t-butyloxycarbonyl-methionine sulfone with isopropyl alcohol using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) followed by deprotection with HCl in EtOAc. NMR (CD₃OD) δ 0.83 (3H, d, J = 6 Hz), 0.94 (3H, t, J = 6 Hz), 1.11-1.56 (2H, m), 1.28 (6H, d, J = 6 Hz), 1.8-1.96 (1H, m), 2.12-2.27 (1H, m), 2.89-3.0 (2H, m), 3.01 (3H, s), 3.06-3.3 (4H, m), 3.42 (1H, dd, J = 6, 13 Hz), 3.65 (1H, dd, J = 6, 13 Hz), 3.68-3.91 (3H, m), 4.2-4.27 (1H, m), 4.61-4.7 (1H, m), 4.96-5.12 (2H, m), 7.19-7.44 (5H, m). Anal. Calc'd. for C₂₆H₄₅N₃O₆S₂ • 2 CF₃CO₂H:

25 C, 44.07; H, 5.67; N, 4.97; Found C, 44.35; H, 5.68; N, 5.23

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EXAMPLE 111-(2(R)-Amino-3-mercaptopropyl)-4-(2,3-dimethylbenzoyl)piperazine dihydrochloride

5

Step A: tert -Butyl 4-(2,3-dimethylbenzoyl)piperazine-1-carboxylate

tert -Butyl piperazine-1-carboxylate (0.50 g, 2.6 mmol), 2,3-dimethylbenzoic acid (0.44 g, 2.9 mmol), 1-hydroxybenzotriazole (HOBT) (0.45 g, 2.9 mmol) and 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (EDC · HCl) (0.56 g, 2.9 mmol) were added to dry, degassed dimethylformamide (7 mL). The pH of the reaction was adjusted to 7 with triethylamine, and the reaction stirred for 2 h. The dimethylformamide (DMF) was distilled *in vacuo*, and the residue partitioned between ethyl acetate and water. The organic phase was washed with 2% aqueous potassium hydrogen sulfate, saturated sodium bicarbonate solution, saturated sodium chloride solution, and dried over magnesium sulfate. The crude product was chromatographed on silica gel using 30% ethyl acetate in hexane as eluant. The title compound was obtained as a white solid, NMR (CDCl₃, 300 MHz) δ 7.17 (1H, d, J=7 Hz), 7.13 (1H, t, J=7 Hz), 6.98 (1H, d, J=7 Hz), 3.77 (2H, m), 3.51 (2H, m), 3.32 (2H, t, J=5 Hz), 3.19 (2H, m), 2.28 (3H, s), 2.18 (3H, s), 1.45 (9H, s).

25 Step B: N-Methoxy-N-methyl 2(R)-tert -butoxycarbonylamino-3-triphenylmethylthiopropionamide

The title compound was synthesized essentially according to the procedure described by O. P. Goel, U. Krolls, M. Stier, and S. Kesten in Organic Syntheses, 1988, 67, 69-75. Thus N,O-dimethyl-hydroxylamine hydrochloride (1.05 g, 10.82 mmol) and N-methyl-morpholine (1.22 mL, 11.14 mmol) were stirred in dichloromethane (6 mL) under nitrogen at 0°C for 30 min. In a separate flask, 2(R)-tert -butoxycarbonylamino-3-triphenylmethyl-thiopropionic acid (5.02 g, 10.82 mmol) in tetrahydrofuran (11.5 mL, dry) and methylene chloride

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(45 mL) were cooled to -20°C , and N-methylmorpholine (1.22 mL, 11.14 mmol) and isopropylchloroformate (10.82 mL of 1M solution in toluene) were added *via* syringe, maintaining the temperature less than -15°C . The reaction was stirred at -30°C , and the suspension of N,O-dimethylhydroxylamine hydrochloride and N-methylmorpholine in methylene chloride added all at once. The cooling bath was removed and the reaction allowed to warm to room temperature over 4 h. The reaction was cooled to 0°C and quickly washed with two portions of 0.2 N hydrochloric acid, two portions of 0.5 N sodium hydroxide, and saturated sodium chloride solution. The organic phase was dried over magnesium sulfate, filtered and reduced *in vacuo* to obtain the title compound as a clear gum. NMR (300 MHz, DMSO- d_6) δ 7.30 (15H, m), 4.43 (1H, br s), 3.56 (3H, s), 2.99 (3H, s), 2.30 (2H, m), 1.36 (9H, s).

15

Step C: 2(R)-*tert* -Butoxycarbonylamino-3-triphenylmethyl-thiopropional

The title compound was synthesized essentially according to the procedure described by O. P. Goel, U. Krolls, M. Stier, and S. Kesten in Organic Syntheses, 1988, 67, 69-75. Thus lithium aluminum hydride (0.451 g, 11.90 mmol) and diethyl ether (40 mL) were stirred at 20°C under nitrogen for 1 h, then cooled to -45°C . N-Methoxy-N-methyl 2(R)-*tert* -butoxycarbonylamino-3-triphenylmethylthiopropionamide (5.50 g, 10.82 mmol) in diethyl ether (20 mL) was added in a steady stream, maintaining the temperature less than -35°C . The cooling bath was removed and the reaction warmed to 5°C , then cooled to -35°C . A solution of potassium hydrogen sulfate (2.94 g, 21.64 mmol) in water (50 mL) was added slowly, maintaining the temperature less than 0°C . The reaction was warmed to 20°C over 1 h, and filtered through Celite. The filtrate was washed with 10% citric acid, saturated sodium chloride solution, and dried over magnesium sulfate. After filtration, the solvents were removed *in vacuo* and the title compound obtained as a foam.

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Step D: 1-(2(R)-*tert* -Butoxycarbonylamino-3-triphenylmethylthiopropyl)-4-(2,3-dimethylbenzoyl)piperazine

The product from step A (0.480 g, 0.860 mmol) was dissolved in methylene chloride (4 mL) and trifluoroacetic acid was added (2 mL). The reaction was stirred for 30 min. at 20°C, then evaporated to dryness. The crude trifluoroacetate salt was taken up in dimethylformamide and the pH adjusted to 6 by the addition of triethylamine. To this solution was added sodium triacetoxyborohydride (0.331 g, 1.56 mmol), and crushed molecular sieves (0.5 g), and the reaction cooled to 0°C under nitrogen. 2(R)-N-*tert* -butoxycarbonylamino-3-triphenylmethylthiopropylal (0.350 g, 0.782 mmol) in dimethylformamide was added slowly dropwise. The reaction was stirred at 20°C under nitrogen for 2 h. The dimethylformamide was removed *in vacuo* and the residue partitioned between saturated sodium bicarbonate and ethyl acetate. The organic phase was washed with saturated sodium chloride and dried over magnesium sulfate. Filtration and evaporation gave the title compound as a white foam. NMR (CDCl₃, 300 MHz) δ 7.0-7.6 (18H, m), 5.60 (1H, br s), 4.4-4.9 (1H, m), 2.1-3.9 (12H, m), 2.25 (3H, s), 2.15 (3H, br s), 1.40 (9H, s).

Step E: 1-(2(R)-Amino-3-mercaptopropyl)-4-(2,3-dimethylbenzoyl)piperazine dihydrochloride

The product from step D and triethylsilane (0.54 mL, 3.4 mmol) were dissolved in methylene chloride (6 mL). To this solution was added trifluoroacetic acid (3 mL) and the reaction stirred at 20°C for 30 min. The reaction was evaporated to dryness and partitioned between hexane and water. The aqueous phase was injected onto a 40 X 100 mm Waters PrepPak[®] reverse phase HPLC column (Delta-Pak[™] C18 15 μ m, 100 Å), and pure product isolated by gradient elution using 100% Solvent A (0.1% trifluoroacetic acid in water) to 50% Solvent A/50% Solvent B (0.1 % trifluoroacetic acid in acetonitrile) over 50 min at a flow rate of 40 mL/min. Combined fractions were evaporated, dissolved in water and passed through a Biorad AG[®] 3X4 ion exchange

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resin column (100-200 mesh, Cl⁻ form). The column eluant was lyophilized to give the title compound as a white powder.

Analysis calculated for C₁₆H₂₅N₃OS • 2.4 HCl • 1.4 H₂O:

C, 45.76; H, 7.25; N, 10.01.

5 Found: C, 45.73, H, 7.25; N, 10.01.

EXAMPLE 12

10 1-[2(R)-Amino-3-mercaptopropyl]-4(S)-(2,3-dimethylbenzoyl)-2-methylpiperazine dihydrochloride

Step A: 1- Benzyl-3(S)-methylpiperazine-2,5-dione

The title compound was prepared according to the procedure described by John S. Kiely and Stephen R. Priebe in *Organic Preparations and Procedures Int.*, 22 (6), 761-768 (1990). Thus 100 mL of a stock solution of dicyclohexylcarbodiimide in methylene chloride (0.5 M) was added to methylene chloride (250 mL). This solution was cooled to 0°C under nitrogen and Boc-L-alanine (9.46 g, 50.00 mmol) was added. The resulting slurry was stirred for 5 min, and then ethyl N-benzylglycinate (9.37 mL, 50.00 mmol) was added. The reaction was stirred for 2 h at 0°C, then at 20°C overnight. The precipitate was removed by filtration, and hydrogen chloride gas bubbled through the methylene chloride solution for 2-4 h, until the reaction was shown to be complete by tlc. The solvent was removed *in vacuo*, and the residue partitioned between ethyl acetate (150 mL) and saturated sodium bicarbonate solution (42 mL). The organic phase was washed with saturated sodium chloride, dried over magnesium sulfate, filtered and evaporated. The crude product was recrystallized from toluene to give the title compound as white crystals. NMR (300 MHz, CDCl₃) δ 7.30-7.38 (3H, m), 7.22-7.30 (2H, m), 6.94 (1H, br s), 4.59 (2H, s), 4.14 (1H, q, J=7 Hz), 3.84 (2H, s), 1.52 (3H, d, J=7 Hz).

Step B: 4-Benzyl-1-tert -butoxycarbonyl-2(S)-methylpiperazine

The product from Step A (5.88 g, 27.00 mmol) was dissolved in THF (200 mL) and cooled under nitrogen to 0°C with

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mechanical stirring. Lithium aluminum hydride (3.69 g, 0.097 mol) was added slowly. The reaction was refluxed for 18 h, cooled to 0°C, and quenched by the sequential slow addition of 5 mL H₂O, 5 mL 10% sodium hydroxide solution and 5 mL H₂O. The reaction was stirred for 30 min and filtered. The solvent was removed *in vacuo*, the crude product taken up in methylene chloride and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate treated with di-*tert*-butyl dicarbonate (6.03 g, 27.6 mmol). After 2 h at 20°C, saturated sodium bicarbonate was added. The layers were separated, and the organic phase washed with saturated sodium chloride solution, then dried over magnesium sulfate. Filtration and evaporation gave the crude product which was purified by column chromatography on silica gel, eluting with 5% ethyl acetate in hexane. The title compound was obtained as a foam. NMR (300 MHz, CDCl₃) δ 7.25 (5H, m), 4.18 (1H, br s), 3.80 (1H, d, J=12 Hz), 3.46 (2H, AB q, J=14 Hz), 3.11 (1H, dt, J=4, 12 Hz), 2.75 (1H, d, J=10 Hz), 2.58 (1H, d, J=10 Hz), 2.12 (1H, dd, J=4, 12 Hz), 2.00 (1H, dt, J=4, 12 Hz), 1.45 (9H, s), 1.23 (3H, d, J=7 Hz).

20 Step C: 1-*tert*-Butoxycarbonyl-2(S)-methylpiperazine

The product from Step B (5.28 g, 18.2 mmol) was dissolved in methanol (75 mL) in a Parr bottle, and the vessel purged with argon. To this was added 10 % palladium on carbon (1.0 g) and the reaction hydrogenated under 60 psi hydrogen for 24 h. The catalyst was removed by filtration through Celite, and the filtrate evaporated *in vacuo* to give the title compound as an oil. NMR (300 MHz, CDCl₃) δ 4.15 (1H, m), 3.77 (1H, d, J=12 Hz), 2.85-3.06 (3H, m), 2.75 (1H, d, J=12 Hz), 2.64 (1H, dt, J=4, 12 Hz), 2.13 (1H, s), 1.45 (9H, s), 1.40 (3H, d, J=7 Hz).

30

Step D: 1-*tert*-Butoxycarbonyl-4-(2,3-dimethylbenzoyl)-2(S)-methylpiperazine

The product from Step C (1.00 g, 5.00 mmol) was converted to the title compound according to the procedure described in

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Example 11, Step A using 2,3-dimethylbenzoic acid (0.750 g, 5.00 mmol), HOBT (0.765 g, 5.00 mmol), EDC • HCl (0.958 g, 5.00 mmol) and triethylamine to adjust the pH to 7. The title compound was obtained as a pale yellow solid.

5

Step E: 1-[2(R)-N-*tert* -Butoxycarbonylamino-3-triphenylmethylthiopropyl]-4-(2,3-dimethylbenzoyl)-2(S)-methylpiperazine

The title compound was obtained from the product of Step D (0.390 g, 1.17 mmol) according to the procedure described in Example 11, Step D. Thus, 1-*tert* -butoxycarbonyl-4-(2,3-dimethylbenzoyl)-2(S)-methylpiperazine (0.390 g, 1.17 mmol) was first treated with trifluoroacetic acid (3 mL) in methylene chloride (6 mL) for 30 min. The reaction was evaporated to dryness, and the crude product reacted with sodium triacetoxyborohydride (0.331 g, 1.56 mmol) and 2(R)-N-*tert* -butoxycarbonylamino-3-triphenylmethylthiopropional (0.350 g, 0.782 mmol) in the presence of crushed molecular sieves (0.5 g) in DMF at pH 6 and 0-20°C overnight. The title compound was obtained as a foam.

20

Step F: 1-[2(R)-Amino-3-mercaptopropyl]-4-(2,3-dimethylbenzoyl)-2(S)-methylpiperazine dihydrochloride

The product from Step E (0.370 g, 0.55 mmol) was converted to the title compound according to the procedure described for Step E, Example 11 using triethylsilane (0.350 mL, 2.20 mmol) and trifluoroacetic acid (4.5 mL) in methylene chloride (9 mL).

Purification by preparative HPLC (gradient elution: 100% Solvent A to 50% Solvent A/50% Solvent B, 50 min) and ion exchange provided the title compound as a white powder.

30 Analysis calculated for C₁₇H₂₇N₃OS • 2.7 HCl • 1.1 H₂O:

C, 46.47; H, 7.32; N, 9.56.

Found: C, 46.40, H, 7.31, N, 9.39.

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EXAMPLE 13

1-[2(R)-Amino-3-mercaptopropyl]-4-(2,3-dimethylbenzoyl)-2(S)-(2-methoxyethyl)piperazine dihydrochloride

5

Step A: 1-Benzyl-3(S)-cyclohexoxycarbonylmethylpiperazine-2,5-dione

The title compound was prepared according to the procedure described in Example 12, Step A, except using Boc-L-aspartic acid, β -cyclohexyl ester (6.15 g, 19.5 mmol), ethyl N-benzylglycinate (3.76 g, 19.5 mmol) and dicyclohexylcarbodiimide (39 mL, 0.5 M in dichloromethane, 19.5 mmol). The title compound was obtained as a white powder. NMR (CD₃OD, 300 MHz) δ 7.3 (5H, m), 4.77 (1H, d, J=15 Hz), 4.73 (1H, m), 4.48 (1H, d, J=15 Hz), 4.35 (1H, t, J=5 Hz), 3.96 (1H, dd, J=1, 17 Hz), 3.87 (1H, dd, J=1, 17 Hz), 3.06 (1H, dd, J=4, 17 Hz), 2.81 (1H, dd, J=5, 17 Hz), 1.78 (4H, m), 1.54 (1H, m), 1.35 (5H, m).

Step B: 4-Benzyl-1-*tert*-butoxycarbonyl-2(S)-(2-hydroxyethyl)piperazine

The title compound was prepared according to the procedure described in Example 12, Step B, except using 1-benzyl-3(S)-cyclohexoxycarbonylmethylpiperazine-2,5-dione (1.5 g, 4.36 mmol) and lithium aluminum hydride (0.76 g, 20.1 mmol), followed by di-*tert*-butyl dicarbonate (1.04 g, 4.77 mmol). The crude product was purified by column chromatography on silica gel, eluting with 30% ethyl acetate in hexane. The title compound was obtained as a clear oil. NMR (CD₃OD, 300 MHz) δ 7.3 (5H, m), 4.20 (1H, m), 3.86 (1H, dm, J=13 Hz), 3.55 (1H, d, J=13 Hz), 3.46 (2H, m), 3.39 (1H, d, J=13 Hz), 3.08 (1H, t, J=12 Hz), 2.80 (1H, d, J=12 Hz), 2.73 (1H, d, J=12 Hz), 2.04 (3H, m), 1.84 (1 H, sextet, J=7 Hz), 1.45 (9H, s).

Step C: 4-Benzyl-1-*tert*-butoxycarbonyl-2(S)-(2-methoxyethyl)piperazine

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A solution of 4-benzyl-1-*tert*-butoxycarbonyl-2(S)-(2-hydroxyethyl)piperazine (0.322 g, 1.00 mmol) in dry, degassed dimethylformamide (4 mL) was cooled under nitrogen to 0°C. Sodium hydride was added (0.052 g, 60% dispersion in oil, 1.30 mmol) followed by methyl iodide (0.88 mL, 1.41 mmol). After 3 h, the reaction was quenched with saturated ammonium chloride. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and saturated sodium bicarbonate. The ethyl acetate was washed with water, saturated sodium chloride solution, and dried over magnesium sulfate. The crude product was chromatographed on silica gel with 40% ethyl acetate in hexane to obtain the title compound as a clear oil. NMR (CD₃OD, 300 MHz) δ 7.3 (5H, m), 4.19 (1H, m), 3.85 (1H, dm, J=13 Hz), 3.56 (1H, d, J=13 Hz), 3.16 (1H, d, J=13 Hz), 3.28 (2H, m, partially obscured by solvent), 3.23 (3H, s), 3.08 (1H, t, J=13 Hz), 2.80 (1H, d, J=11 Hz), 2.70 (1H, d, J=11 Hz), 2.03 (3H, m), 1.86, (1H, sextet, J=6 Hz), 1.45 (9H, s).

Step D: 1-*tert*-Butoxycarbonyl-2(S)-(2-methoxyethyl)piperazine

The title compound was prepared according to the procedure described in Example 12, Step C, except using 4-benzyl-1-*tert*-butoxycarbonyl-2(S)-(2-methoxyethyl)piperazine (0.280 g, 0.83 mmol) and 10% palladium on carbon (80 mg). The title compound was obtained as an oil. NMR (CD₃OD, 300 MHz) δ 4.17 (1H, m), 3.81 (1H, dd, J=3, 13 Hz), 3.38 (2H, t, J=6 Hz), 2.82-3.02 (2H, m), 2.77 (2H, ABq, J=4, 13 Hz), 2.59 (1H, dt, J=4, 7 Hz), 2.04 (1H, m), 1.84 (1H, m), 1.46 (9H, s).

Step E: 1-*tert*-Butoxycarbonyl-4-(2,3-dimethylbenzoyl)-2(S)-(2-methoxyethyl)piperazine

The title compound was prepared according to the procedure described for Example 11, Step A except using 1-*tert*-butoxycarbonyl-2(S)-(2-methoxyethyl)piperazine (0.179 g, 0.73 mmol), 2,3-dimethylbenzoic acid (0.115 g, 0.75 mmol), HOBT (0.098 g, 0.73 mmol), EDC•HCl (0.153 g, 0.80 mmol) in methylene chloride (5 mL).

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Triethylamine was added to adjust the pH to 7. Chromatography on silica gel with 40% ethyl acetate in hexane afforded the title compound as a clear oil. NMR (CDCl₃, 300 MHz) δ 6.9-7.2 (5H, m), 4.70 (1H, m), 3.8-4.5 (9H, mm), 2.0-2.3 (6H, mm), 1.9 (2H, m), 1.59 (9H, s).

5

Step F: 1-[2(R)-N-*tert*-Butoxycarbonylamino-3-triphenylmethylthiopropyl]-4-(2,3-dimethylbenzoyl)-2(S)-(2-methoxyethyl)piperazine

The title compound was prepared according to the procedure described in Example 11, Step D, except using 1-*tert*-butoxycarbonyl-4-(2,3-dimethylbenzoyl)-2(S)-(2-methoxyethyl)piperazine (0.222 g, 0.590 mmol) and trifluoroacetic acid (3 mL) in methylene chloride (7 mL). The trifluoroacetate salt was reacted with 2(R)-N-*tert*-butoxycarbonylamino-3-triphenylmethylthiopropional (0.316 g, 0.710 mmol), sodium triacetoxyborohydride (0.565 g, 2.65 mmol) in the presence of crushed molecular sieves in dichloroethane. The title compound was isolated after chromatography on silica gel with 50% ethyl acetate in hexane.

20 Step G: 1-[2(R)-Amino-3-mercaptopropyl]-4-(2,3-dimethylbenzoyl)-2(S)-(2-methoxyethyl)piperazine dihydrochloride

The title compound was obtained according to the procedure described for Step E, Example 11 except using 1-[2(R)-N-*tert*-butoxycarbonylamino-3-triphenylmethylthiopropyl]-4-(2,3-dimethylbenzoyl)-2(S)-(2-methoxyethyl)piperazine (0.247 g, 0.349 mmol), triethylsilane (0.22 mL, 1.39 mmol) and trifluoroacetic acid (3.5 mL) in methylene chloride (7 mL). Purification by preparative HPLC (gradient elution: 95% Solvent A to 30% Solvent A/70% Solvent B, 60 min) and ion exchange provided the title compound as a white powder.

30

Analysis calculated for C₁₉H₃₁N₃OS • 3.80 HCl • 0.6 H₂O:

C, 44.39; H, 7.06; N, 8.17.

Found: C, 44.46; H, 7.07; N, 8.00.

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EXAMPLE 145 1-[2(R)-Amino-3-mercaptopropyl]-4-(2,3-dimethylbenzoyl)-2(S)-(2-methylthioethyl)piperazine dihydrochlorideStep A: 1-Benzyl-3(S)-(2-methylthioethyl)piperazine-2,5-dione

The title compound was prepared according to the procedure described in Example 12, Step A, except using Boc-L-methionine (10.0 g, 40.0 mmol), ethyl N-benzylglycinate (7.75 g, 40.0 mmol), HOBT (5.41 g, 40.0 mmol) and EDC · HCl (7.68 g, 40.0 mmol) in dimethylformamide. Upon completion of the reaction, the dimethylformamide was removed *in vacuo* and the crude product partitioned between ethyl acetate and water. The organic phase was washed with water and saturated sodium chloride solution, then dried over sodium sulfate. The solvent was removed *in vacuo* and the residue taken up in methylene chloride (200 mL). Trifluoroacetic acid (100 mL) was added and the reaction stirred at 20°C for 2 h. The volatiles were removed *in vacuo* and the residue partitioned between ethyl acetate and saturated sodium bicarbonate solution.. The organic phase was washed with saturated sodium chloride solution and dried over magnesium sulfate. The title compound was obtained as a white solid. NMR (CHCl₃, 300 MHz) δ 7.4-7.2 (6H, m); 4.60 (2H, AB q, J= 13 Hz); 4.24 (1H, m); 3.85 (2H, AB q, J= 18 Hz); 2.63 (2H, t, J= 7Hz); 2.3-2.1 (2H, m); 2.1 (3H, s).

Step B: 4- Benzyl-1-tert -butoxycarbonyl-2(S)-(2-methylthioethyl)piperazine

The title compound was prepared according to the procedure described in Example 12, Step B, except using 1-benzyl-3(S)-(2-methylthioethyl)piperazine-2,5-dione (9.08 g, 32.6 mmol) and lithium aluminum hydride (4.40 g, 0.115 mmol), followed by di-tert -butyl dicarbonate (7.64 g, 35.0 mmol). The crude product was purified by column chromatography on silica gel, eluting with 5% ethyl acetate

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in hexane. The title compound was obtained as a clear oil. NMR (CHCl₃, 300 MHz) δ 7.35-7.25 (5H, m); 4.18 (1H, br s); 3.90 (1H, br d); 3.55 (1H, d, J= 13Hz); 3.40 (1H, d, J= 13Hz); 3.07 (1H, t, J= 12 Hz); 2.72 (2H, m); 2.40 (2H, m); 2.10 (3H, s); 1.48 (9H, s).

5

Step C: 1-*tert* - Butoxycarbonyl-2(S)-(2-methylthioethyl)piperazine

To a solution of the product from Step B (6.63 g, 18.9 mmol) in 20 mL methylene chloride was added 2.15 mL (20 mmol) of 10 1-chloroethyl chloroformate (ACE-Cl) dropwise with stirring. The temperature rose from 25 °C to 32 °C. After 90 min was added another 0.20 mL of ACE-Cl and 2.4 g of solid potassium carbonate. After 90 min the mixture was diluted with ethyl acetate and washed successively with 10% sodium bicarbonate and brine. The solution was dried 15 (sodium sulfate) and evaporated to afford 8.4 g of an oil. The oil was dissolved in 500 mL methanol. The mixture was stirred at room temperature for 3 h and placed in the refrigerator overnight. The solution was treated with 100 mL of water and the methanol was evaporated. The solution was washed with ethyl acetate to remove 20 nonbasic impurities. The aqueous phase was neutralized with 10% sodium bicarbonate and extracted with methylene chloride. The extract was dried (potassium carbonate) and evaporated to give 4.0 g of 1-*tert* -butoxycarbonyl-2(S)-(2-methylthioethyl)piperazine. NMR (CHCl₃, 300 MHz) δ 4.17 (1H, br s); 3.89 (1H, br d); 2.92 (4H, m); 2.70 (1H, dt, J= 25 4,12 Hz); 2.6-2.4 (2H, m); 2.10 (3H, s); 1.88 (1H, m); 1.48 (9H,s).

Step D: 1-*tert* -Butoxycarbonyl-4-(2,3-dimethylbenzoyl)-2(S)-(2-methylthioethyl)piperazine

The title compound was prepared according to the 30 procedure described for Example 11, Step A except using 1-*tert* -butoxycarbonyl-2(S)-(2-methylthioethyl)piperazine (1.87 g, 7.19 mmol), 2,3-dimethylbenzoic acid (1.08 g, 7.19 mmol), HOBT (0.970 g, 7.19 mmol), EDC•HCl (1.64 g, 8.62 mmol) in methylene chloride (50 mL). Triethylamine was added to adjust the pH to 7. Chromatography

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on silica gel with 30% ethyl acetate in hexane afforded the title compound as a clear oil. NMR (DMSO-d₆, 300 MHz) δ 6.9-7.3 (3H, m), 4.22-4.50 (2H, mm), 3.62-4.06 (2H, mm), 2.66-3.24 (4H, mm), 2.4 (1H, m), 2.24 (3H, s), 1.92-2.18 (6H, ms), 1.4-1.8 (2H, m), 1.39 (9H, s).

5

Step E: 1-[2(R)-N-*tert* -Butoxycarbonylamino-3-triphenylmethylthiopropyl]-4-(2,3-dimethylbenzoyl)-2(S)-(2-methylthioethyl)piperazine

The title compound was prepared according to the procedure described in Example 11, Step D, except using 1-*tert* -butoxycarbonyl-4-(2,3-dimethylbenzoyl)-2(S)-(2-methylthioethyl)piperazine (0.465 g, 1.18 mmol) and trifluoroacetic acid (3 mL) in methylene chloride (7 mL). The trifluoroacetate salt was reacted with 2(R)-N-*tert* -butoxycarbonylamino-3-triphenylmethylthiopropional (0.400 g, 0.890 mmol), sodium triacetoxyborohydride (0.302 g, 1.42 mmol) in the presence of crushed molecular sieves in dichloroethane. The title compound was isolated as a foam after chromatography on silica gel with 50% ethyl acetate in hexane.

20 Step F: 4-[2(R)-Amino-3-mercaptopropyl]-1-(2,3-dimethylbenzoyl)-2(S)-(2-methylthioethyl)piperazine dihydrochloride

The title compound was obtained according to the procedure described for Step E, Example 11 except using 1-[2(R)-N-*tert* -butoxycarbonylamino-3-triphenylmethylthiopropyl]-4-(2,3-dimethylbenzoyl)-2(S)-(2-methylthioethyl)piperazine (0.465 g, 0.656 mmol), triethylsilane (0.420 mL, 2.63 mmol) and trifluoroacetic acid (3.5 mL) in methylene chloride (7 mL). Purification by preparative HPLC (gradient elution: 95% Solvent A to 20% Solvent A/80% Solvent B, 60 min) and ion exchange provided the title compound as a white powder.

Analysis calculated for C₁₉H₃₁N₃OS₂ • 2.80 HCl • 0.8 H₂O:
C, 45.85; H, 7.17; N, 8.44.
Found: C, 45.85; H, 7.14; N, 8.32.

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EXAMPLE 15

1-[2(R)-Amino-3-mercaptopropyl]-4-(1-naphthoyl)-2(S)-(2-methoxyethyl)piperazine dihydrochloride (Compound E)

5

Step A: 4-Benzyl-1-[2(R)-*tert*-butoxycarbonylamino-3-triphenylmethylthiopropyl]-2(S)-(2-methoxyethyl)piperazine

4-Benzyl-1-*tert*-butoxycarbonyl-2(S)-(2-methoxyethyl)-piperazine from Example 13, step C (1.17 g, 3.50 mmol) was dissolved in methylene chloride (20 mL). To this solution was added trifluoroacetic acid (10 mL) and the reaction stirred at 20°C for 1 h. The volatiles were removed in vacuo and the residue taken up in dichloroethane (40 mL). Triethylamine was added to attain pH 7. To this solution was added crushed molecular sieves (1 g), sodium triacetoxyborohydride (1.2 g, 5.3 mmol) and the reaction cooled to -15°C with ice-methanol. A solution of 2(R)-*tert*-butoxycarbonylamino-3-triphenylmethylthiopropylaldehyde (1.72 g, 3.85 mmol) in dichloroethane (15 mL) was added slowly dropwise. The reaction was stirred at 20°C overnight then quenched with saturated sodium bicarbonate. The organic phase was washed with saturated sodium chloride solution, and dried over magnesium sulfate. The crude product (2.52 g) was chromatographed on silica gel with 30% ethyl acetate in hexane using medium pressure liquid chromatography (MPLC). The title compound (*R_f* 0.21) was isolated as a gum. NMR (CHCl₃, 300 MHz) δ 7.2-7.4 (20 H, m), 4.70 (1H, d, *J*=8 Hz), 3.63 (1H, br s), 3.50 (1H, d, *J*=13 Hz), 3.36 (1H, d, *J*=13 Hz), 3.2-3.35 (5H, m), 2.75 (1H, m), 2.0-2.6 (10 H, m), 1.75 (2H, m), 1.42 (9H, s). A diastereomeric minor product (*R_f* 0.14) was also isolated.

30 Step B: 1-[2(R)-*tert*-Butoxycarbonylamino-3-triphenylmethylthiopropyl]-2(S)-(2-methoxyethyl)piperazine

The title compound was obtained by treating the product of step A (0.884 g, 1.33 mmol) with 1-chloroethyl chloroformate (0.151 mL, 1.39 mmol) and potassium carbonate (0.200 g, 1.45 mmol) in

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dichloromethane (15 mL) according to the procedure described in Example 14, step C. The crude product was chromatographed on silica gel with 5-10% methanol in chloroform. The title compound was isolated as a foam. NMR (CHCl₃, 300 MHz) δ 7.2-7.45 (15H, m), 4.66 (1H, d, J=8 Hz), 3.65 (1H, m), 3.35 (2H, m), 3.28 (3H, s), 2.94 (1H, dd, J=12, 3 Hz), 1.7-2.9 (13H, m), 1.42 (9H, s).

Step C: 1-[2(R)-*tert*-Butoxycarbonylamino-3-triphenylmethyl-thiopropyl]-2(S)-(2-methoxyethyl)-4-(1-naphthoyl)-piperazine

The title compound was prepared from the product of Step B (0.422 g, 0.733 mmol), 1-naphthoic acid (0.120 mg, 0.698 mmol), EDC • HCl (0.154 mg, 0.806 mmol), HOBT (0.099 g, 0.733 mmol) in DMF at pH 7 according to the procedure described in Example 11, Step A. The crude product was chromatographed on silica gel with 30-40% ethyl acetate in hexane (R_f 0.50, 40% ethyl acetate/hexane). The title compound was isolated as a gum.

Step D: 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(2-methoxyethyl)-4-(1-naphthoyl)piperazine dihydrochloride

The title compound was prepared from the product of Step C (0.438 g, 0.600 mmol), triethylsilane (0.383 mL, 2.4 mmol), trifluoroacetic acid (10 mL) in dichloromethane (20 mL) according to the procedure described in Example 11, Step E. The crude product was purified by preparative HPLC (gradient: 85% Solvent A/15% Solvent B to 65% Solvent A/35% Solvent B). After ion exchange and lyophilization, the title compound was obtained as a white powder.

Analysis calculated for C₂₁H₂₉N₃O₂S • 2.95 HCl • 0.05 H₂O:
C, 50.85; H, 6.51; N, 8.47.
Found: C, 50.86; H, 6.12; N, 8.31.

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EXAMPLE 16

Preparation of N-[2(S)-N'-(1-(4-Nitrophenylmethyl)-1H-imidazol-4-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine bis trifluoroacetate and N-[2(S)-N'-(1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine bis trifluoroacetate

10 Step A: Preparation of 1-(4-Nitrophenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester and 1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetic acid methyl ester (3:1 mixture)

To a solution of sodium hydride (60% in mineral oil, 99 mg, 2.5 mmol) in dimethylformamide (2 ml) cooled to 0°C was added, via cannula, a solution of 1H-imidazole-4-acetic acid methyl ester hydrochloride (200 mg, 1.13 mmol) in dimethylformamide (3 ml). This suspension was allowed to stir at 0°C for 15 min. To this suspension was added 4-nitrobenzyl bromide (244 mg, 1.13 mmol) and stirred at room temperature for 2 h. After this time, the mixture was quenched with sat. aq. sodium bicarbonate (15 ml) and water (20 ml) and extracted with methylene chloride (2 x 50 ml). The combined organic extracts were washed with brine (20 ml), dried (MgSO₄), filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography using acetonitrile as eluent to give the title compounds as a yellow oil.

25 ¹H NMR (CDCl₃, 400 MHz) δ 8.20 (2H, d, J=8.5 Hz), 7.49 (1H, s), 7.27 (2H, d, J=8.5 Hz), 7.03 (0.25H, s), 6.87 (0.75H, s), 5.28 (0.5H, s), 5.18 (1.5H, s), 3.70 (2.25H, s), 3.65 (1.5H, s), 3.61 (0.75H, s) and 3.44 (0.5H, s) ppm.

30 Step B: Preparation of 1-(4-Nitrophenylmethyl)-1H-imidazol-4-ylacetic acid hydrochloride and 1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetic acid (3:1 mixture)

To a solution of a mixture of 1-(4-Nitrophenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester and 1-(4-Nitrophenylmethyl)-1H-

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imidazol-5-ylacetic acid methyl ester (3:1 mixture, 216 mg, 0.785 mmol) in methanol (3 ml) and tetrahydrofuran (3 ml) under argon was added 1.0 M sodium hydroxide (1.18 ml, 1.18 mmol) and stirred for 18 h.

After this time, 1.0 N hydrochloric acid (2.36 ml, 2.36 mmol) was

5 added and the mixture evaporated *in vacuo* to give the title compounds.

¹H NMR (CDCl₃, 400 MHz) δ 9.04 (0.75H, s), 8.83 (0.25H, s), 8.28 (2H, d, J=8.8 Hz), 7.61 (2H, d, J=8.8 Hz), 7.54 (0.75H, s), 7.43 (0.25H, s), 5.61 (0.5H, s), 5.58 (1.5H, s), 3.84 (0.5H, s) and 3.82 (1.5H, s) ppm.

10 Step C: Preparation of N-[(2S)-N'-(1-(4-Nitrophenylmethyl)-1H-imidazol-4-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester bis trifluoroacetate and N-[2(S)-N'-(1-(4-Nitrophenyl-methyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester bis

15 trifluoroacetate

To a solution of 1-(4-nitrophenylmethyl)-1H-imidazol-4-ylacetic acid hydrochloride and 1-(4-nitrophenylmethyl)-1H-imidazol-5-ylacetic acid hydrochloride (3:1 mixture, 153 mg, 0.392 mmol), N-[2(S)-amino-3(S)-methylpentyl]-N-naphthylmethyl-glycyl-methionine methyl ester bis hydrochloride (209 mg, 0.392 mmol) and 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOBT, 64 mg, 0.39 mmol) in methylene chloride (10 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 75.2 mg, 0.392 mmol) and triethylamine (219 µl, 1.57 mmol) and the mixture stirred overnight at room temperature. After this time, sat. aq. sodium bicarbonate (10 ml) was added and the mixture was extracted with methylene chloride. The combined extracts were washed with sat. aq. sodium bicarbonate (10 ml) and the solvent evaporated *in vacuo*. The regioisomers were separated

20 by Prep HPLC using a Nova Prep 5000 Semi preparative HPLC system and a Waters PrepPak cartridge (47 X 300mm, C18, 15 µm, 100A) eluting with 5 - 95% acetonitrile/water (0.1% TFA) at 100 ml/min (chromatography method A) to give after lyophilization **Compounds F and G.**

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F:

¹H NMR (CD₃OD, 400 MHz) δ 8.96 (1H, s), 8.17 (1H, m), 8.23 (2H, d, J=8.7 Hz), 7.92 (2H, d, J=8.9 Hz), 7.61 (1H, d, J=6.9 Hz), 7.56 (2H, d, J=8.9 Hz), 7.50 (2H, m), 7.44 (2H, m), 5.52 (2H, s), 4.70 (1H, d, J=9.4 Hz), 4.49 (1H, d, J=11.9 Hz), 4.38 (1H, dd, J=4.7 and 8.9 Hz), 4.13 (1H, m), 3.67 (3H, s), 3.65 (4H, m), 3.30 (1H, m), 3.06 (1H, m), 2.31 (1H, m), 2.23 (1H, m), 1.97 (3H, s), 1.94 (1H, m), 1.71 (1H, m), 1.57 (1H, m), 1.42 (1H, m), 1.17 (1H, m), 0.90 (3H, d, J=6.9 Hz) and 0.87 (3H, t, J=7.4 Hz) ppm.

Anal. Calcd for C₃₇H₄₆N₆O₆S•2.40 TFA•0.25 H₂O: C, 51.18; H, 5.02; N, 8.57. Found: C, 51.17; H, 5.03; N, 8.80.

FAB MS calcd for C₃₇H₄₇N₆O₆S 703 (MH⁺), found 703.

G:

¹H NMR (CD₃OD, 400 MHz) δ 8.91 (1H, s), 8.26 (1H, d, J=12.8 Hz), 8.21 (2H, d, J=10.7 Hz), 7.91 (2H, m), 7.65-7.36 (7H, m), 5.51 (2H, s), 4.72-3.99 (4H, m), 3.66 (3H, s), 3.66-3.24 (4H, m), 3.20-2.85 (2H, m), 2.29 (1H, m), 2.20 (1H, m), 1.96 (3H, s), 1.91 (1H, br s), 1.70 (1H, d, J=16 Hz), 1.56 (1H, m), 1.38 (1H, m), 1.13 (1H, m) and 0.88 (6H, m) ppm.

FAB HRMS exact mass calcd for C₃₇H₄₇N₆O₆S 703.32778 (MH⁺), found 703.32852.

25 Step D: Preparation of N-[2(S)-N'-(1-(4-Nitrophenylmethyl)-1H-imidazol-4-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine bis trifluoroacetate

To a solution of N-[2(S)-N'-(1-(4-nitrophenylmethyl)-1H-imidazol-4-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester bis trifluoroacetate (F, 21 mg, 0.023 mmol) in methanol (1 ml) at room temperature was added 1.0N lithium hydroxide (135 μl, 0.135 mmol). This solution was stirred for 4 h and treated with trifluoroacetic acid (100 μl). This mixture was purified by

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preparative HPLC using chromatography method A to give the title compound.

¹H NMR (CD₃OD, 400 MHz) δ 8.86 (1H, s), 8.23 (2H, d, J= 8.8Hz), 8.22 (1H, m), 7.90 (2H, dd, J=7.3 Hz), 7.55 (2H, d, J=8.4 Hz), 7.44-7.28 (5H, m), 5.50 (2H, s), 4.53 (1H, m), 4.35 (2H, m), 4.12 (1H, m), 3.79-3.25 (4H, m), 3.26-2.86 (2H, m), 2.27 (1H, m), 2.18 (1H, m), 1.96 (3H, s), 1.9 (1H, m), 1.67 (1H, m), 1.57 (1H, m), 1.42 (1H, m), 1.15 (1H, m), 0.90 (3H, d, J=6.9 Hz) and 0.86 (3H, t, J=7.3 Hz) ppm.
FAB HRMS exact mass calcd for C₃₆H₄₅N₆O₆S 689.31213 (MH⁺),
found 689.31262.

Step E: Preparation of N-[2(S)-N'-(1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine bis trifluoroacetate

To a solution of N-[2(S)-N'-(1-(4-nitrophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester bis trifluoroacetate (29 mg, 0.031 mmol) in methanol (1 ml) was added 1.0N lithium hydroxide (187 µl, 0.187 mmol). This solution was stirred for 4 h and treated with trifluoroacetic acid (100 µl). This mixture was purified by preparative HPLC using chromatography method A to give the title compound.
¹H NMR (CD₃OD, 400 MHz) δ 8.89 (1H, s), 8.25 (1H, m), 8.21 (2H, d, J= 9.0Hz), 7.89 (2H, m), 7.64-7.34 (7H, m), 5.52 (2H, s), 4.59-3.88 (4H, m), 3.77-3.38 (4H, m), 3.18-2.75 (2H, m), 2.27 (1H, m), 2.18 (1H, m), 1.96 (3H, s), 1.9 (1H, m), 1.67 (1H, m), 1.57 (1H, m), 1.42 (1H, m), 1.15 (1H, m), 0.89 (6H, m) ppm.
FAB HRMS exact mass calcd for C₃₆H₄₅N₆O₆S 689.31213 (MH⁺),
found 689.31135.

30

EXAMPLE 17

Regioselective preparation of N-[2(S)-N'-(1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester bis trifluoroacetate

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Step A: Preparation of 1-(Triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester

To a suspension of 1H-imidazole-4-acetic acid methyl ester hydrochloride (7.48, 42.4 mmol) in methylene chloride (200 ml) was added triethylamine (17.7 ml, 127 mmol) and triphenylmethyl bromide (16.4 g, 50.8 mmol) and stirred for 72 h. After this time, reaction mixture was washed with sat. aq. sodium bicarbonate (100 ml) and water (100 ml). The organic layer was evaporated *in vacuo* and purified by flash chromatography (30-100% ethyl acetate/hexanes gradient elution) to provide the title compound as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.35 (1H, s), 7.31 (9H, m), 7.22 (6H, m), 6.76 (1H, s), 3.68 (3H, s) and 3.60 (2H, s) ppm.

Step B: Preparation of 1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetic acid methyl ester

To a solution of 1-(triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester from Step A (274 mg, 0.736 mmol) in acetonitrile (10 ml) was added 4-nitrobenzylbromide (159 mg, 0.736 mmol) and heated to 55°C for 16 h. After this time, the reaction was cooled to room temperature, treated with ethyl acetate (20 ml) and the resulting precipitate was filtered. The filtrate was concentrated to dryness *in vacuo* and the residue was redissolved in acetonitrile (4 ml) and heated to 65°C for 3 h. After this time, the reaction mixture was evaporated to dryness and combined with initial precipitate. This residue was dissolved in methanol (5 ml) and heated to reflux for 30 min. The resulting solution was evaporated *in vacuo* and the residue was purified by flash chromatography (2-5% methanol/methylene chloride gradient elution) to provide the title compound. ¹H NMR (CDCl₃, 400 MHz) δ 8.20 (2H, d, J=8.8 Hz), 7.53 (1H, s), 7.19 (2H, d, J=8.8 Hz), 7.03 (1H, s), 5.28 (2H, s), 3.61 (3H, s) and 3.44 (2H, s) ppm.

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Step C: Preparation of 1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetic acid hydrochloride

1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetic acid methyl ester (0.115 g, 0.42 mmol) was dissolved in 1.0N hydrochloric acid (10 ml) and heated at 55°C for 3 h. The solution was evaporated *in vacuo* to give the title compound as a white solid.

¹H NMR (CD₃OD, 400 MHz) δ 9.06 (1H, s), 8.27 (2H, d, J=8.8 Hz), 7.61 (1H, s), 7.55 (2H, d, J=8.8 Hz), 5.63 (2H, s) and 3.81 (2H, s) ppm.

10 Step D: Preparation of N-[2(S)-N'-(1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester bis trifluoroacetate

15 Following the procedure described in Example 16, Step C, but using the 1-(4-nitrophenylmethyl)-1H-imidazol-5-ylacetic acid hydrochloride, prepared as described in Step C provided the title compound.

EXAMPLE 18

20

Preparation of N-[2(S)-N'-(1-(4-Cyanophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine bis trifluoroacetate (Compound B)

25 Step A: Preparation of N-[2(S)-N'-(1-(4-Cyanophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester bis trifluoroacetate

30 Following the procedure described in Example 17, Steps B-D, but using α-bromo-p-tolunitrile in place of 4-nitrobenzylbromide provided the title compound.

¹H NMR (CD₃OD, 400 MHz) δ 8.92 (1H, s), 8.31 (1H, m), 8.01 (1H, d, J=8 Hz), 7.96 (1H, m), 7.75 (2H, d, J=8 Hz), 7.62 (1H, s), 7.58-7.48 (3H, m), 7.45 (1H, m), 7.41 (2H, d, J=8 Hz), 5.51 (2H, s), 4.97 (1H, m),

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4.76 (1H, m), 4.41 (1H, m), 4.10 (1H, m) 3.92 (2H, m), 3.75-3.47 (3H, m), 3.69 (3H, s), 3.25 (1H, m), 2.37 (1H, m), 2.30 (1H, m), 2.00 (3H, s), 1.97 (1H, m), 1.79 (1H, m), 1.58 (1H, m), 1.43 (1H, m), 1.19 (1H, m) and 0.91 (6H, m) ppm.

- 5 Anal. Calcd for $C_{38}H_{46}N_6O_4S \cdot 2.40 \text{ TFA} \cdot 1.90 \text{ H}_2\text{O}$: C, 51.89; H, 5.31; N, 8.48. Found: C, 51.88; H, 5.29; N, 8.72.

FAB HRMS exact mass calcd for $C_{38}H_{47}N_6O_4S$ 683.337951 (MH^+), found 683.338437.

10

EXAMPLE 19

In vitro inhibition of ras farnesyl transferase

- Assays of farnesyl-protein transferase.* Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and RAS-CAIL) is prepared as described by Schaber *et al.*, *J. Biol. Chem.* 265:14701-14704 (1990), Pompliano, *et al.*, *Biochemistry* 31:3800 (1992) and Gibbs *et al.*, *PNAS U.S.A.* 86:6630-6634 (1989), respectively. Bovine FPTase is assayed in a volume of 100 μ l containing 100 mM *N*-(2-hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM $MgCl_2$, 5 mM dithiothreitol (DTT), 100 mM [3H]-farnesyl diphosphate ([3H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 μ g/ml FPTase at 31°C for 60 min. Reactions are initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol. Precipitates are collected onto filter-mats using a TomTec Mach II cell harvester, washed with 100% ethanol, dried and counted in an LKB β -plate counter. The assay is linear with respect to both substrates, FPTase levels and time; less than 10% of the [3H]-FPP is utilized during the reaction period. Individual purified protein substrate-competitive inhibitor and/or farnesyl pyrophosphate-competitive inhibitor and compositions of the invention that comprise at least one of a protein substrate-competitive inhibitor and a farnesyl pyrophosphate-competitive inhibitor are dissolved in 100% dimethyl sulfoxide (DMSO) and are diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound

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when compared to the amount of incorporation in the absence of the test compound.

Human FPTase is prepared as described by Omer *et al.*, *Biochemistry* 32:5167-5176 (1993). Human FPTase activity is assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 μ M ZnCl₂ and 100 nM Ras-CVIM are added to the reaction mixture. Reactions are performed for 30 min., stopped with 100 μ l of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

Comparison is made between the inhibitory activity of a composition of the instant invention and the inhibitory activities of individual compounds that make up the composition in the assay.

EXAMPLE 20

In vivo ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. *et al.*, *Cancer Research* 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemented with 10% regular DMEM, 2% fetal bovine serum and 400 mCi[³⁵S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl₂/1mM DTT/10 μ g/ml aprotinen/2 μ g/ml leupeptin/2 μ g/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are brought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. *et al.*, *J. Virol.* 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG

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is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 mM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

Comparison is made between the inhibitory activity of a composition of the instant invention and the inhibitory activities of individual compounds that make up the composition in the assay.

EXAMPLE 21

15

In vivo ras farnesylation assay

The cell line used in this assay is a H-ras line derived from a NIH3T3 cells, which expressed cellular Ha-ras p21. The assay is performed essentially as described in Ana Maria Garcia et al., The Journal of Biological Chemistry 268:18415-18418, (1993). Cells in 3.3 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, dimethyl sulfoxide, is 0.1%). After 24 hours the cells are lysed in lysis buffer (1% NP40/20mM HEPES, pH 7.5/5mM MgCl₂/1 µg/ml aprotinin/2 µg/ml leupeptin/2 µg/ml antipain/0.5mM PMSF). The lysate was separated by centrifugation at 13000rpm for 5 min and the supernatant used as cell extract. Total protein was separated by SDS-polyacrylamide gel electrophoresis in 12% acrylamide gels. After transfer to nitrocellulose, the blots were probed with NCC-RAS-004 mouse monoclonal antibody to H-ras (Nihonkayaku). All Western blots were developed using enhanced chemiluminescence reagents (Amersham Corp.). The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

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Comparison is made between the inhibitory activity of a composition of instant of instant invention and the inhibitory activities of individual compounds that make up the composition in the assay.

5

EXAMPLE 22

In vivo growth inhibition assay

To determine the biological consequences of FPTase inhibition, the effect of examples of compositions of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a *v-ras*, *v-raf*, or *v-mos* oncogene in comparison with the effect of the individual components of such compositions on the same growth was tested. Cells transformed by v-Raf were included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation. Cells transformed by v-Mos may also be included in an analysis.

Rat 1 cells transformed with either *v-ras* or *v-raf* were seeded at a density of 1×10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contained 0.1% methanol or an appropriate concentration of the instant composition or the individual component compounds (dissolved in methanol at 1000 times the final concentration used in the assay). The cells were fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs were taken 9 days after the cultures are seeded and comparisons are made between treated and untreated plates.

The results of the assay are shown in Table 1. The extent of inhibition of the cell growth was inferred from the subjective quantization of the colony growth. Wild type (vehicle only) colony growth is designated "+/++", less than wild type growth is designated "+", much less than wild type growth is designated "+/-" and no visually

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detectable colonies is designated "-". The assay was run against individual protein substrate-competitive FPTase inhibitors (Compounds A and B) and a farnesyl pyrophosphate-competitive FPTase inhibitor (Compound C) to establish minimum concentrations where wild type or
5 less than wild type growth was observed. The compositions containing both the protein substrate-competitive and farnesyl pyrophosphate-competitive inhibitors were then tested in the assay at those concentrations of the FPTase inhibitors that showed such non-inhibitory or minimally inhibitory effects for the individual compounds.

10

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TABLE 1

	<u>Compound</u>	<u>Conc. μM</u>	<u>Ras</u>	<u>Raf</u>
5	MeOH		+/++	+/++
	Compound A	2.5	+/-	+/++
		1	+/-	+/++
		0.25	+/++	+/++
10				
	Compound B	2.5	-	+/++
		1	-	+/++
		0.25	+	+/++
15				
	Compound C	10	+	+/++
		2.5	+/++	+/++
		1	+/++	+/++
20				
	Compound C	at 2.5	+/- to +	+/++
	Compound A	at 0.25		
25				
	Compound C	at 2.5	- to +/-	+/++
	Compound B	at 0.25		
30				
35				

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WHAT IS CLAIMED IS:

1. A method for achieving an additive or synergistic therapeutic effect in a mammal in need thereof which comprises
5 administering to said mammal amounts of at least two therapeutic agents selected from a group consisting of:

- 10 a) a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to the protein substrate of the enzyme and
b) a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to farnesyl pyrophosphate;

15 wherein the amount of a) alone and the amount of b) alone is insufficient to achieve said therapeutic effect.

2. The method according to Claim 1 wherein an amount
20 of a protein substrate-competitive inhibitor and an amount of a farnesyl pyrophosphate-competitive inhibitor are administered simultaneously.

3. A method for achieving a synergistic therapeutic effect in a mammal in need thereof which comprises administering to
25 said mammal amounts of at least two therapeutic agents selected from a group consisting of:

- 30 a) a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to the protein substrate of the enzyme and
b) a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to farnesyl pyrophosphate;

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wherein the amount of a) alone and the amount of b) alone is insufficient to achieve said therapeutic effect; and wherein said therapeutic effect of the amounts of the therapeutic agents administered is greater than the sum of the therapeutic effects of the amounts of the amounts of the individual therapeutic agents administered.

4. The method according to Claim 3 wherein an amount of a protein substrate-competitive inhibitor and an amount of a farnesyl pyrophosphate-competitive inhibitor are administered simultaneously.

5. The method according to Claim 1 wherein the protein substrate-competitive inhibitor is selected from:

a) a peptide that comprises the amino acids CA₁A₂X, wherein:

C = cysteine;

A₁ = an aliphatic amino acid;

A₂ = an aliphatic amino acid; and

X = any amino acid;

20

b) Cys - Xaa¹ - Xaa² - Xaa³ - NRR¹, wherein

Cys = cysteine;

Xaa¹ = any amino acid in the natural L-isomer form;

Xaa² = any amino acid in the natural L-isomer form; and

25

Xaa³ - NRR¹ = an amide of any amino acid in the natural L-isomer form, wherein R and R¹ are independently selected from hydrogen, C₁-C₁₂ alkyl, aralkyl, or unsubstituted or substituted aryl;

30 c) Cys - Xaa¹ - Xaa² - Xaa³, wherein

Cys = cysteine;

Xaa¹ = any amino acid;

Xaa² = the amino acid phenyl alanine or a p-fluorophenylalanine; and

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Xaa³ = any amino acid;

d) Cys - Xaa¹ - dXaa² - Xaa³, wherein

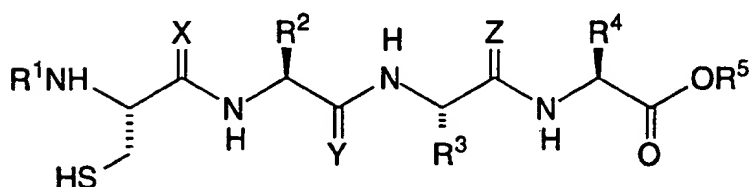
Cys = cysteine;

5 Xaa¹ = any amino acid in the natural L-isomer form;

dXaa² = any amino acid in the natural L-isomer form; and

Xaa³ = any amino acid in the natural L-isomer form;

e)



10

wherein:

X, Y, and Z are independently H₂ or O, provided that at least one of these is H₂;

15 R¹ is H, an alkyl group, an acyl group, an alkylsulfonyl group or aryl sulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms, or in the alternative, R¹NH may be absent;

20

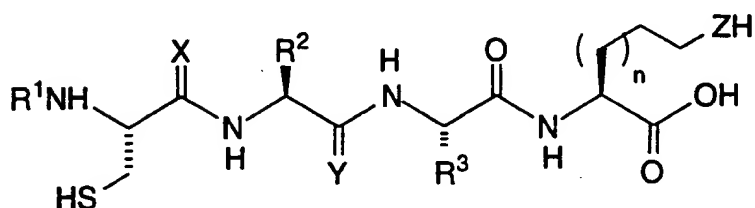
R², R³ and R⁴ are the side chains of naturally occurring amino acids, or in the alternative may be substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl or saturated chains of 2 to 8 carbon atoms, wherein the aliphatic substituents may be substituted with an aromatic or heteroaromatic ring; and

25

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R^5 is H or a straight or branched chain aliphatic group, which may be substituted with an aromatic or heteroaromatic group;

5 f)



wherein:

X and Y are independently H_2 or O, provided that at least one of these is H_2 ;

10

R^1 is H, an alkyl group, an acyl group, an alkylsulfonyl group or aryl sulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms, or in the alternative, R^1NH may be absent;

15

R^2 and R^3 are the side chains of naturally occurring amino acids, or in the alternative may be substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl or saturated chains of 2 to 8 carbon atoms, wherein the aliphatic substituents may be substituted with an aromatic or heteroaromatic ring;

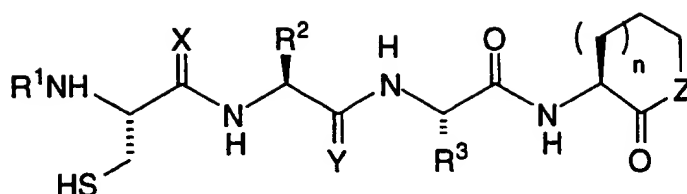
20

25 Z is O or S; and

n is 0, 1 or 2;

g)

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wherein:

X and Y are independently H₂ or O, provided that at least one of these is H₂;

5

R¹ is H, an alkyl group, an acyl group, an alkylsulfonyl group or aryl sulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms, or in the alternative, R¹NH may be absent;

10

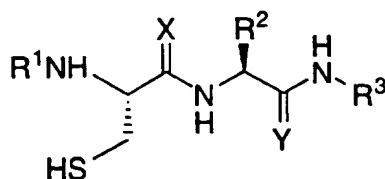
R² and R³ are the side chains of naturally occurring amino acids, or in the alternative may be substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl or saturated chains of 2 to 8 carbon atoms, wherein the aliphatic substituents may be substituted with an aromatic or heteroaromatic ring;

15

20 Z is O or S; and

n is 0, 1 or 2;

h)



25

wherein:

X and Y are independently H₂ or O;

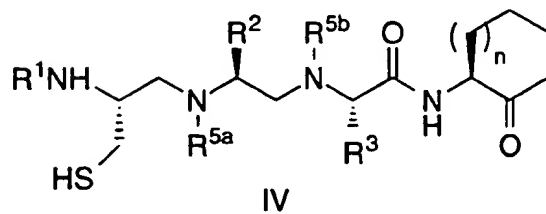
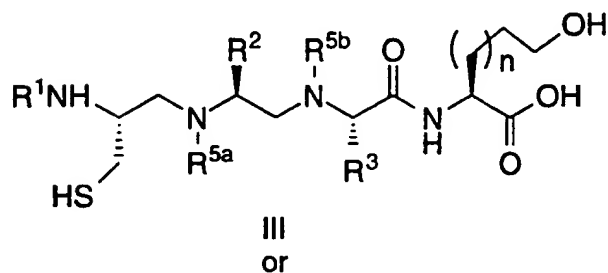
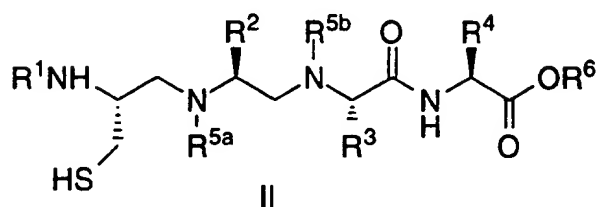
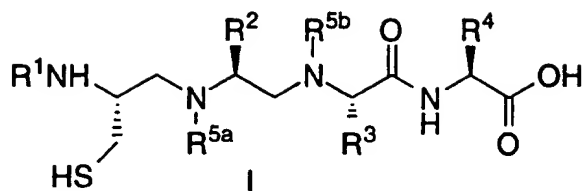
5 R¹ is an alkyl group, hydrogen, an acyl group, an alkylsulfonyl group or arylsulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbons atoms, which alternatively may be substituted with an aryl group;

10 R² is the side chains of naturally occurring amino acids, or in the
alternative may be substituted or unsubstituted aliphatic,
aromatic or heterocyclic groups, such as allyl, cyclohexyl,
phenyl, pyridyl, imidazolyl or saturated chains of 2 to 8
15 carbon atoms which may be branched or unbranched,
wherein the aliphatic substituents may be substituted with an
aromatic or heteroaromatic ring;

20 R³ is an aromatic or heteroaromatic ring or in the alternative an alkyl group or an aryl or heteroaryl substituted alkane, wherein the aromatic ring is unsubstituted or in the alternative, substituted with one or more groups which may be alkyl, halo, alkoxy, trifluoromethyl, or sulfamoyl groups, and which may be polycyclic;

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i)



5 wherein:

R^1 and R^{5a} are independently selected from:
hydrogen, a C1-C6 alkyl group, a C1-C6 acyl group, an
aroyl group, a C1-C6 alkylsulfonyl group, C1-C6
aralkylsulfonyl group or arylsulfonyl group

10

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wherein the alkyl group and acyl group is optionally substituted with substituted or unsubstituted aryl or heterocycle;

5 R², R³ and R⁴ are independently selected from:

a) a side chain of naturally occurring amino acids,
b) an oxidized form of a side chain of naturally occurring amino acids selected from methionine sulfoxide and methionine sulfone,

10 c) substituted or unsubstituted C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₂-C₈ alkenyl, aryl or heterocycle groups, wherein the aliphatic substituent is optionally substituted with an aryl, heterocycle or C₃-C₈ cycloalkyl;

15 R^{5b} is a C₁-C₆ alkyl group, a C₁-C₆ acyl group, an aroyl group, a C₁-C₆ alkylsulfonyl group, C₁-C₆ aralkylsulfonyl group or arylsulfonyl group

20 wherein the alkyl group and acyl group is optionally substituted with substituted or unsubstituted aryl or heterocycle;

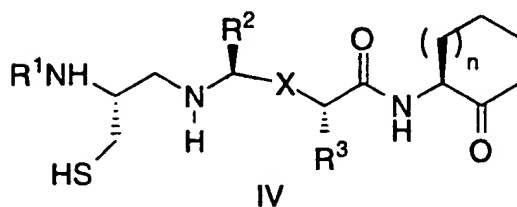
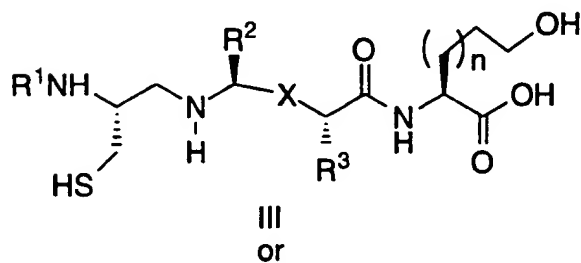
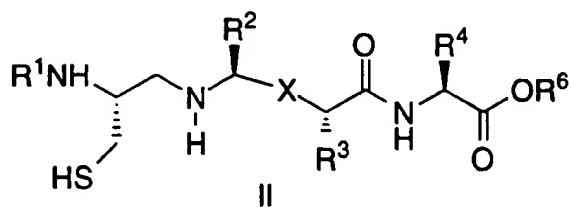
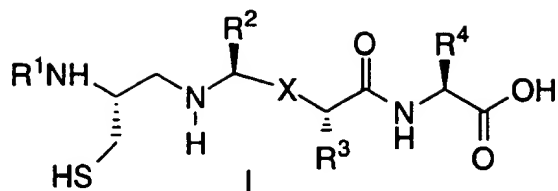
R⁶ is a substituted or unsubstituted aliphatic, aryl or heterocyclic group, wherein the aliphatic substituent is optionally substituted with an aryl or heterocyclic ring; and

25

n is 0, 1 or 2;

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j)



5

wherein:

R¹ is selected from:

10

hydrogen, a C₁-C₆ alkyl group, a C₁-C₆ acyl group, an
 aroyl group, a C₁-C₆ alkylsulfonyl group, C₁-C₆
 aralkylsulfonyl group or arylsulfonyl group

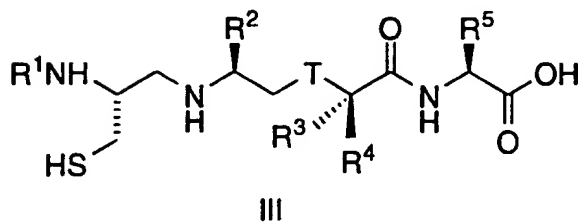
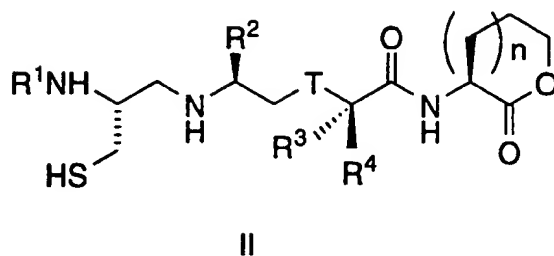
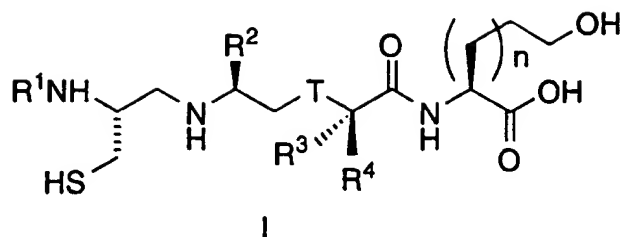
- 398 -

wherein the alkyl group and acyl group is optionally substituted with substituted or unsubstituted aryl or heterocycle;

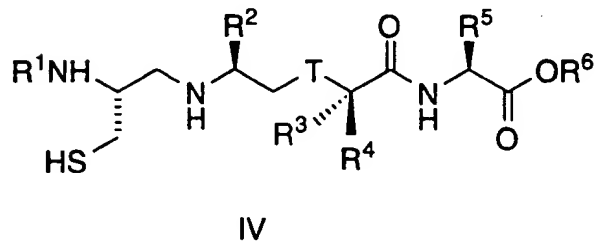
- 5 R^2 , R^3 and R^4 are independently selected from:
- a) a side chain of naturally occurring amino acids,
 - b) an oxidized form of a side chain of naturally occurring amino acids selected from methionine sulfoxide and methionine sulfone,
 - 10 c) substituted or unsubstituted C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₂-C₈ alkenyl, aryl or heterocycle groups, wherein the aliphatic substituent is optionally substituted with an aryl, heterocycle or C₃-C₈ cycloalkyl;
- 15 X is CH₂CH₂ or trans CH=CH;
- R^6 is a substituted or unsubstituted aliphatic, aryl or heterocyclic group, wherein the aliphatic substituent is optionally substituted with an aryl or heterocyclic ring; and
- 20 n is 0, 1 or 2;

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k)



or



5 wherein,

R¹ is hydrogen, an alkyl group, an aralkyl group, an acyl group,
an aracyl group, an aroyl group, an alkylsulfonyl group,

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aralkylsulfonyl group or arylsulfonyl group, wherein alkyl and acyl groups comprise straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms;

5 R², R³ and R⁵ are
the side chains of naturally occurring amino acids,
including their oxidized forms which may be methionine
sulfoxide or methionine sulfone, or in the alternative may
be substituted or unsubstituted aliphatic, aromatic or
10 heteroaromatic groups, such as allyl, cyclohexyl, phenyl,
pyridyl, imidazolyl or saturated chains of 2 to 8 carbon
atoms which may be branched or unbranched, wherein the
aliphatic substituents may be substituted with an aromatic or
heteroaromatic ring;

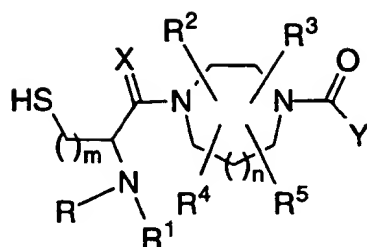
15 R⁴ is hydrogen or an alkyl group, wherein the alkyl group
comprises straight chain or branched chain hydrocarbons of
1 to 6 carbon atoms;

20 R⁶ is a substituted or unsubstituted aliphatic, aromatic or
heteroaromatic group such as saturated chains of 1 to 8
carbon atoms, which may be branched or unbranched,
wherein the aliphatic substituent may be substituted with an
aromatic or heteroaromatic ring;

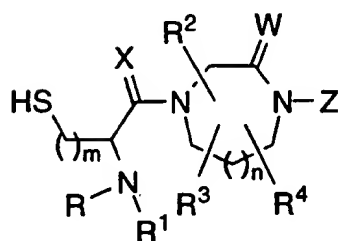
25 T is O or S(O)_m;
 m is 0, 1 or 2; and
 n is 0, 1 or 2;

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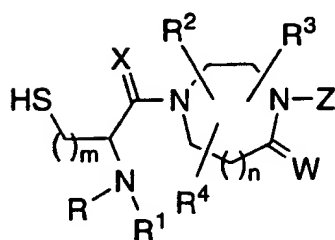
I)



A



B



C

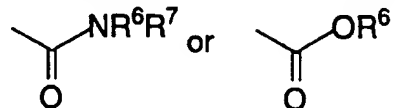
wherein:

- 5 X is O or H₂;
 m is 1 or 2;
 n is 0 or 1;
 t is 1 to 4;
 R and R¹ are independently selected from H, C₁-4 alkyl, or aralkyl;

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R^2 , R^3 , R^4 , and R^5 are independently selected from: H; C₁-8 alkyl,

alkenyl, alkynyl, aryl, heterocycle,
 unsubstituted or substituted with one or more of:



5

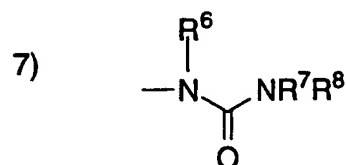
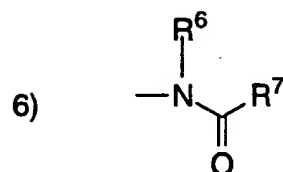
1) aryl or heterocycle, unsubstituted or substituted with:

- a) C₁-4 alkyl,
- b) $(\text{CH}_2)_t\text{OR}^6$,
- c) $(\text{CH}_2)_t\text{NR}^6\text{R}^7$,
- d) halogen,

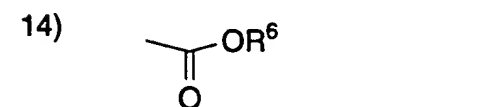
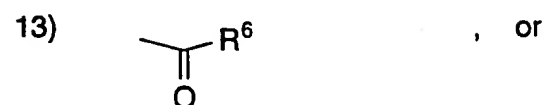
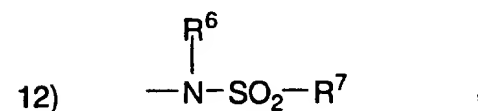
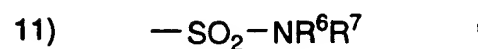
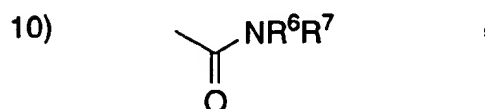
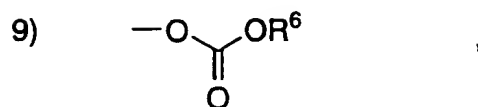
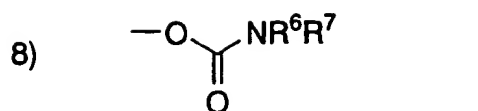
10

- 2) C₃-6 cycloalkyl,
- 3) OR^6 ,
- 4) SR^6 , S(O)R^6 , SO_2R^6 ,

5) $-\text{NR}^6\text{R}^7$,



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and any two of R^2 , R^3 , R^4 , and R^5 are optionally attached to the

5

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

10

1) C₁₋₄ alkyl, unsubstituted or substituted with:

- a) C₁₋₄ alkoxy,
- b) NR^6R^7 ,
- c) C₃₋₆ cycloalkyl,
- d) aryl or heterocycle,
- e) HO,

15

- 2) aryl or heterocycle,
- 3) halogen,
- 4) OR^6 ,

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- 5) NR^6R^7 ,
- 6) CN ,
- 7) NO_2 , or
- 8) CF_3 ;

5

W is H_2 or O;

Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

10

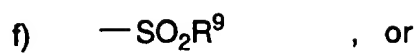
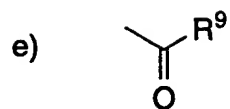
- 1) C_{1-4} alkyl, unsubstituted or substituted with:
 - a) C_{1-4} alkoxy,
 - b) NR^6R^7 ,
 - c) C_{3-6} cycloalkyl,
- 15 d) aryl or heterocycle, or
- e) HO ,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) OR^6 ,
- 20 5) NR^6R^7 ,
- 6) CN ,
- 7) NO_2 , or
- 8) CF_3 ;

25 R^6 , R^7 and R^8 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

30

- a) C_{1-4} alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO ,

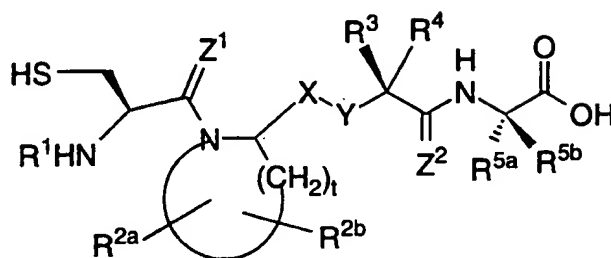
- 405 -



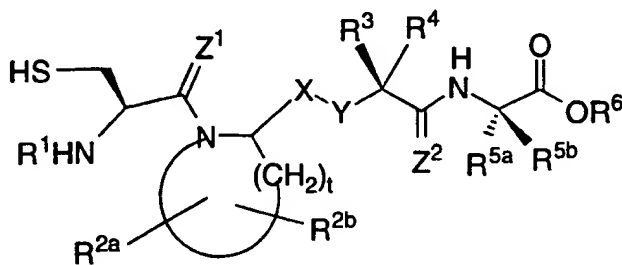
g) NRR^1 , wherein

- 5 R^6 and R^7 may be joined in a ring, and
 R^7 and R^8 may be joined in a ring; and
 R^9 is C_{1-4} alkyl or aralkyl;

m)

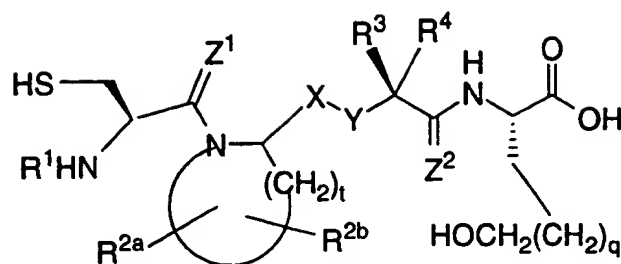
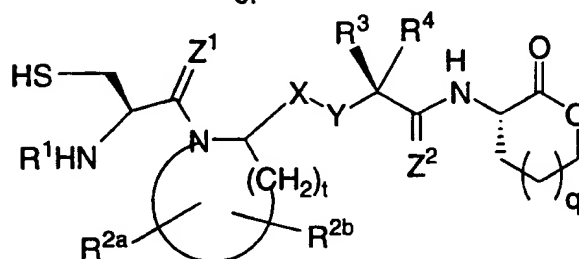


I



II

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III
or

IV

wherein:

R¹ is selected from:

- a) hydrogen,
- 5 b) R⁸S(O)₂-, R⁸C(O)-, (R⁸)₂NC(O)- or R⁹OC(O)-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, R⁸O-, R⁸S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-;
- 10

R^{2a} and R^{2b} are independently selected from:

- a) hydrogen,
- 15 b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R⁸O-, R⁸S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-,
- c) aryl, heterocycle, cycloalkyl, alkenyl, R⁸O-, R⁸S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
- 20

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d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

5 R³ and R⁴ are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

10 ii) methionine sulfone, and

c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,

wherein the substituent is selected from F,

Cl, Br, N(R⁸)₂, NO₂, R⁸O-, R⁸S(O)_m-,

15 R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-,

R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂,

R⁹OC(O)NR⁸- and C₁-C₂₀ alkyl, and

d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and
20 C₃-C₁₀ cycloalkyl; or

R³ and R⁴ are combined to form - (CH₂)_s - ;

R^{5a} and R^{5b} are independently selected from:

25 a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

30 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,

wherein the substituent is selected from F, Cl, Br, N(R⁸)₂, NO₂, R⁸O-, R⁸S(O)_m-, R⁸C(O)NR⁸-, CN,

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$(R^8)_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3 ,
 $-N(R^8)_2$, $R^9OC(O)NR^8-$ and C_1-C_{20} alkyl, and

d) C_1-C_6 alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocyclic and
 C_3-C_{10} cycloalkyl; or

5

R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of
 the carbon atoms is optionally replaced by a moiety selected
 from: O, $S(O)_m$, $-NC(O)-$, and $-N(COR^8)-$;

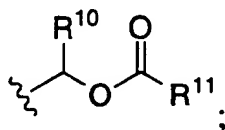
10 R^6 is

a) substituted or unsubstituted C_1-C_8 alkyl, wherein the
 substituent on the alkyl is selected from:

- 1) aryl,
- 2) heterocycle,
- 3) $-N(R^9)_2$,
- 4) $-OR^8$, or

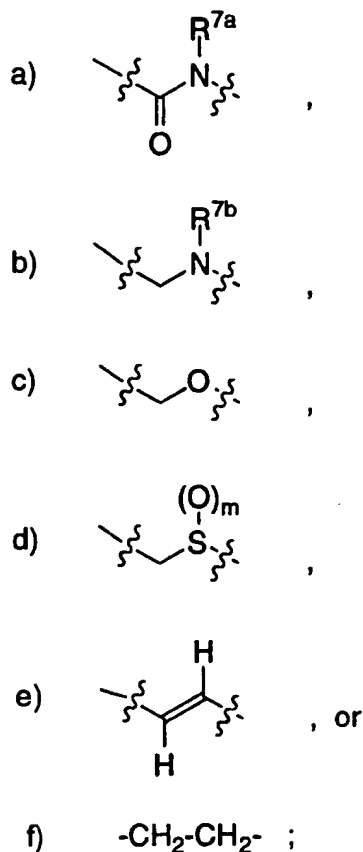
15

b)



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X-Y is

R^{7a} is selected from

5

- a) hydrogen,
 - b) unsubstituted or substituted aryl,
 - c) unsubstituted or substituted heterocycle,
 - d) unsubstituted or substituted cycloalkyl, and
 - e) C₁-C₆ alkyl substituted with hydrogen or an
- 10 unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl;

R^{7b} is selected from

15

- a) hydrogen,
- b) unsubstituted or substituted aryl,

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- 5 c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted cycloalkyl,
e) C₁-C₆ alkyl substituted with hydrogen or an
unsubstituted or substituted group selected from aryl,
heterocycle and cycloalkyl,
f) a carbonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocycle,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
an unsubstituted or substituted group selected from aryl,
heterocycle and cycloalkyl, and
10 g) a sulfonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocycle,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
an unsubstituted or substituted group selected from aryl,
heterocycle and cycloalkyl;
15

R⁸ is independently selected from hydrogen, C₁-C₆ alkyl and aryl;

20 R⁹ is independently selected from C₁-C₆ alkyl and aryl;

R¹⁰ is independently selected from hydrogen and C₁-C₆ alkyl;

R¹¹ is independently selected from C₁-C₆ alkyl;

25 Z¹ and Z² are independently H₂ or O, provided that Z¹ is not O
when

X-Y is - C(O)N(R^{7a})-;

30 m is 0, 1 or 2;

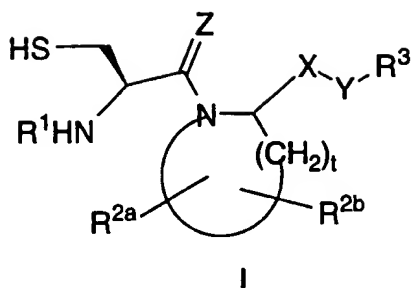
q is 0, 1 or 2;

s is 4 or 5; and

t is 3, 4 or 5;

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n)



wherein:

5 R¹ is selected from:

- a) hydrogen,
 - b) R⁵S(O)₂-, R⁵C(O)-, (R⁵)₂NC(O)- or R⁶OC(O)-, and
 - c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
- 10 heterocyclic, cycloalkyl, alkenyl, alkynyl, R⁵O-, R⁵S(O)_m-, R⁵C(O)NR⁵-, CN, (R⁵)₂N-C(NR⁵)-, R⁵C(O)-, R⁵OC(O)-, N₃, -N(R⁵)₂, or R⁶OC(O)NR⁵-;

R^{2a} and R^{2b} are independently selected from:

- 15 a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R⁵O-, R⁵S(O)_m-, R⁵C(O)NR⁵-, CN, (R⁵)₂N-C(NR⁵)-, R⁵C(O)-, R⁵OC(O)-, N₃, -N(R⁵)₂, or R⁶OC(O)NR⁵-, and
- 20 c) aryl, heterocycle, cycloalkyl, alkenyl, R⁵O-, R⁵S(O)_m-, R⁵C(O)NR⁵-, CN, NO₂, (R⁵)₂N-C(NR⁵)-, R⁵C(O)-, R⁵OC(O)-, N₃, -N(R⁵)₂, or R⁶OC(O)NR⁵-;

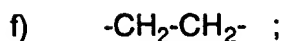
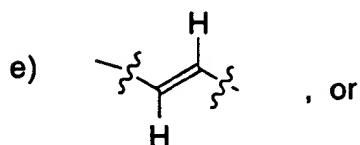
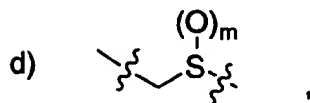
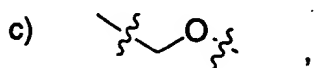
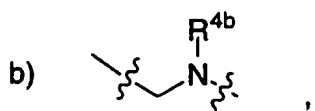
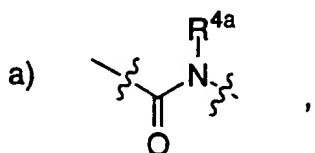
R³ is selected from:

- 25 a) unsubstituted or substituted aryl,
- b) unsubstituted or substituted heterocycle,
- c) unsubstituted or substituted cycloalkyl, and

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d) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl;

X-Y is



R^{4a} is selected from

10

a) hydrogen,

b) unsubstituted or substituted aryl,

c) unsubstituted or substituted heterocycle,

d) unsubstituted or substituted cycloalkyl, and

15

e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl;

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R^{4b} is selected from

- a) hydrogen,
- b) unsubstituted or substituted aryl,
- 5 c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted cycloalkyl,
- e) C₁-C₆ alkyl substituted with hydrogen or an
unsubstituted or substituted group selected from aryl,
heterocycle and cycloalkyl,
- 10 f) a carbonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocycle,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
an unsubstituted or substituted group selected from aryl,
heterocycle and cycloalkyl, and
- 15 g) a sulfonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocycle,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
an unsubstituted or substituted group selected from aryl,
heterocycle and cycloalkyl;

20

R⁵ is independently selected from hydrogen, C₁-C₆ alkyl and aryl;

R⁶ is independently selected from C₁-C₆ alkyl and aryl;

25 Z is independently H₂ or O;

m is 0, 1 or 2, provided that m is 0 when R⁵ = hydrogen ;

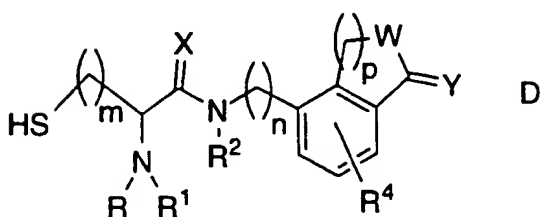
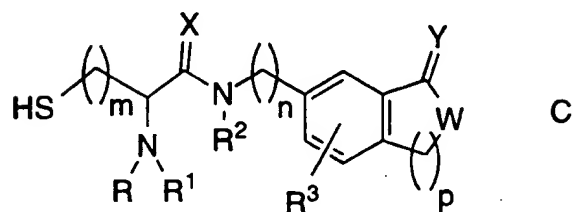
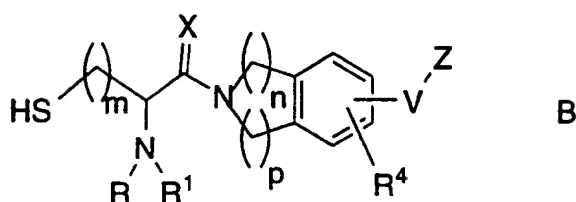
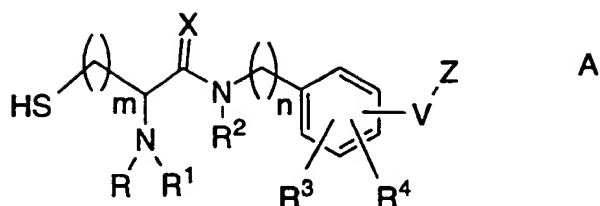
n is 0, 1, 2, 3 or 4; and

t is 3, 4 or 5;

30

- 414 -

p)



wherein:

- 5 X and Y are independently O or H₂;
 m is 1 or 2;
 n is 0 or 1;
 p is 1, 2 or 3;
 q is 0, 1 or 2;
 10 t is 1 to 4;
 R, R¹ and R² are independently selected from: H, C₁-6 alkyl, or C₁-6 aralkyl;

- 415 -

R³ and R⁴ are independently selected from:

- 5
- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, R⁶O-, R⁵S(O)_q-, R⁷C(O)NR⁶-, CN, N₃, R⁶OC(O)NR⁶-, R⁶R⁷N-C(NR⁶R⁸)-, R⁶C(O)-, R⁷R⁸NC(O)O-, R⁷R⁸NC(O)-, R⁶R⁷N-S(O)₂-, -NR⁶S(O)₂R⁵, R⁶OC(O)O-, -NR⁶R⁷, or R⁷R⁸NC(O)NR⁶-,
- 10
- c) unsubstituted or substituted cycloalkyl, alkenyl, R⁶O-, R⁵S(O)_q-, R⁶C(O)NR⁶-, CN, NO₂, R⁶R⁷N-C(NR⁸)-, R⁶C(O)-, N₃, -NR⁶R⁷, halogen or R⁷OC(O)NR⁶-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

15

W is -CHR⁹- or -NR⁹- ;

Z is unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle;

20

wherein the substituted group is substituted with one or more of:

- 1) C₁-4 alkyl, unsubstituted or substituted with:
- 25
- a) C₁-4 alkoxy,
- b) NR⁶R⁷,
- c) C₃-6 cycloalkyl,
- d) aryl or heterocycle,
- e) HO,
- 2) aryl or heterocycle,
- 3) halogen,
- 30
- 4) OR⁶,
- 5) NR⁶R⁷,
- 6) CN,
- 7) NO₂, or
- 9) CF₃;

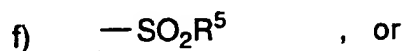
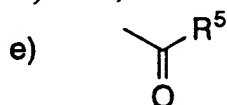
- 416 -

R⁵ is C₁-4 alkyl or aralkyl;

R⁶, R⁷ and R⁸ are independently selected from: H, C₁-4 alkyl, C₃-6
5 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl,
heteroarylsulfonyl, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO,

10

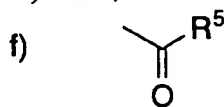


R⁶ and R⁷ may be joined in a ring, and
15 R⁷ and R⁸ may be joined in a ring;

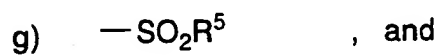
R⁹ is selected from: H, C₁-4 alkyl, C₃-6 cycloalkyl, heterocycle and
aryl, unsubstituted, monosubstituted or disubstituted with
substituents independently selected from:

20

- a) C₁-4 alkyl,
- b) C₁-4 alkoxy,
- c) aryl or heterocycle,
- d) halogen,
- e) HO,



25



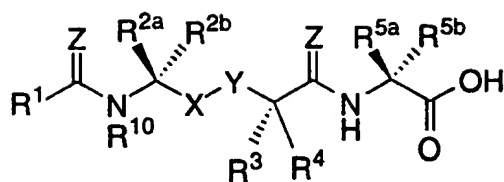
- 417 -

V is selected from: $-C(R^{11})=C(R^{11})-$, $-C\equiv C-$, $-C(O)-$, $-C(R^{11})_2-$,
5 $-C(OR^{11})R^{11}-$, $-CN(R^{11})_2R^{11}-$, $-OC(R^{11})_2-$, $-NR^{11}C(R^{11})_2-$,
 $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C(O)NR^{11}-$, $-NR^{11}C(O)-$, O,
 $-NC(O)R^{11}-$, $-NC(O)OR^{11}-$, $-S(O)_2N(R^{11})-$, $-N(R^{11})S(O)_2-$, or
 $S(O)_m$;

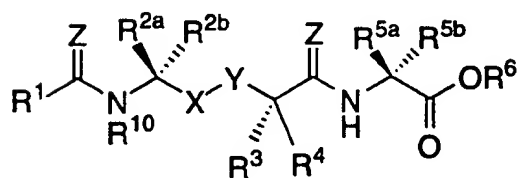
R^{10} and R^{11} are independently selected from hydrogen, C_1 - C_6 alkyl,
 C_2 - C_4 alkenyl, benzyl and aryl;

- 418 -

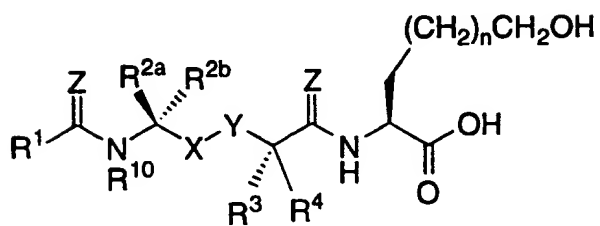
q)



I

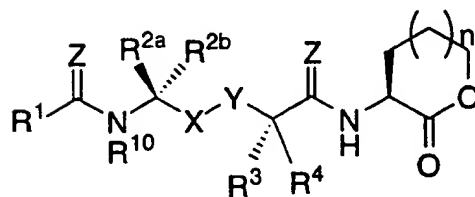


II



III

or



IV

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R¹ is selected from:

- 5 a) heterocycle, and
 b) C₁-C₁₀ alkyl, which is substituted with heterocycle and
 which is optionally substituted with one or more of C₁-C₄
 alkyl, hydroxy or amino groups;

R^{2a} and R^{2b} are independently selected from:

- 10 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally
 occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀
15 alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 NO₂, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-
 C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂,
 R⁹OC(O)NR⁸- and C₁-C₂₀ alkyl, and
20 d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and
 C₃-C₁₀ cycloalkyl; or

R^{2a} and R^{2b} are combined to form - (CH₂)_s - ;

25

R³ and R⁴ are independently selected from:

- 30 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring
 amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone, and
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀
 alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,

- 420 -

5 wherein the substituent is selected from F, Cl, Br, $N(R^8)_2$, NO_2 , R^8O- , $R^9S(O)_m-$, $R^8C(O)NR^8-$, CN , $(R^8)_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3 , $-N(R^8)_2$, $R^9OC(O)NR^8-$ and C1-C20 alkyl, and
d) C1-C6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C3-C10 cycloalkyl; or

10 R^3 and R^4 are combined to form $-(CH_2)_s-$;

R^{5a} and R^{5b} are independently selected from:

- 15 a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
i) methionine sulfoxide, or
ii) methionine sulfone,
c) substituted or unsubstituted C1-C20 alkyl, C2-C20 alkenyl, C3-C10 cycloalkyl, aryl or heterocycle group,
wherein the substituent is selected from F, Cl, Br,
20 $N(R^8)_2$, NO_2 , R^8O- , $R^9S(O)_m-$, $R^8C(O)NR^8-$, CN , $(R^8)_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3 , $-N(R^8)_2$, $R^9OC(O)NR^8-$ and C1-C20 alkyl, and
d) C1-C6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C3-C10 cycloalkyl; or
- 25

R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, $-NC(O)-$, and $-N(COR^8)-$;

30

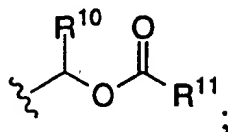
R^6 is

- a) substituted or unsubstituted C1-C8 alkyl, wherein the substituent on the alkyl is selected from:
1) aryl,

- 421 -

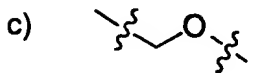
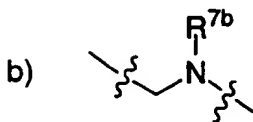
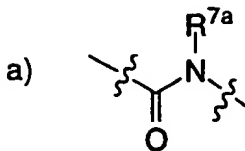
- 2) heterocycle,
- 3) $-N(R^9)_2$,
- 4) $-OR^8$, or

b)

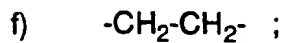
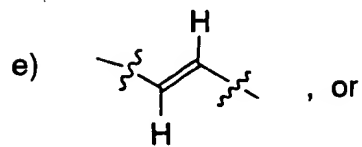
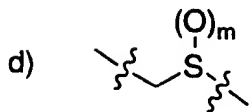


5

X-Y is



10

R^{7a} is selected from

- a) hydrogen,

- 422 -

- 5 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocyclic,
 d) unsubstituted or substituted cycloalkyl, and
 e) C₁-C₆ alkyl substituted with hydrogen or an
 unsubstituted or substituted group selected from aryl,
 heterocyclic and cycloalkyl;

R^{7b} is selected from

- 10 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocyclic,
 d) unsubstituted or substituted cycloalkyl,
 e) C₁-C₆ alkyl substituted with hydrogen or an
 unsubstituted or substituted group selected from aryl,
15 heterocyclic and cycloalkyl,
 f) a carbonyl group which is bonded to an unsubstituted or
 substituted group selected from aryl, heterocyclic,
 cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an
 unsubstituted or substituted group selected from aryl,
20 heterocyclic and cycloalkyl, and
 g) a sulfonyl group which is bonded to an unsubstituted or
 substituted group selected from aryl, heterocyclic,
 cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an
 unsubstituted or substituted group selected from aryl,
25 heterocyclic and cycloalkyl;

R⁸ is independently selected from hydrogen, C₁-C₆ alkyl and aryl;

R⁹ is independently selected from C₁-C₆ alkyl and aryl;

30

R¹⁰ is independently selected from hydrogen and C₁-C₆ alkyl;

R¹¹ is independently selected from C₁-C₆ alkyl;

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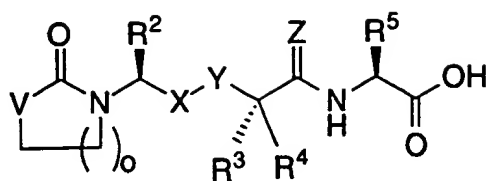
Z is independently H₂ or O;

m is 0, 1 or 2;

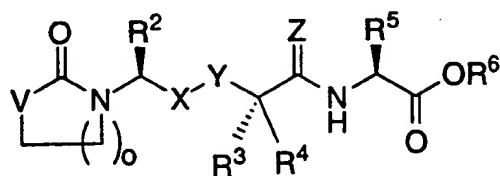
n is 0, 1 or 2; and

5 s is 4 or 5;

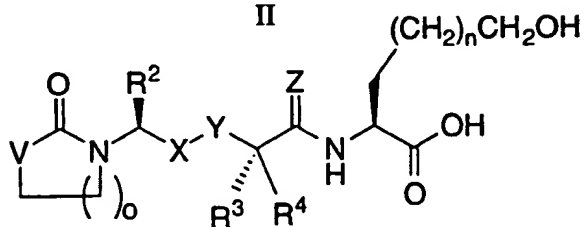
r)



I

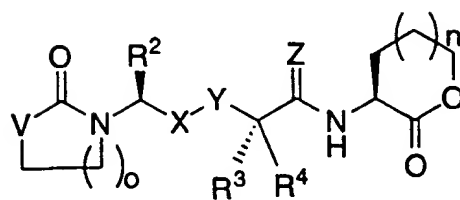


II



III

and



IV

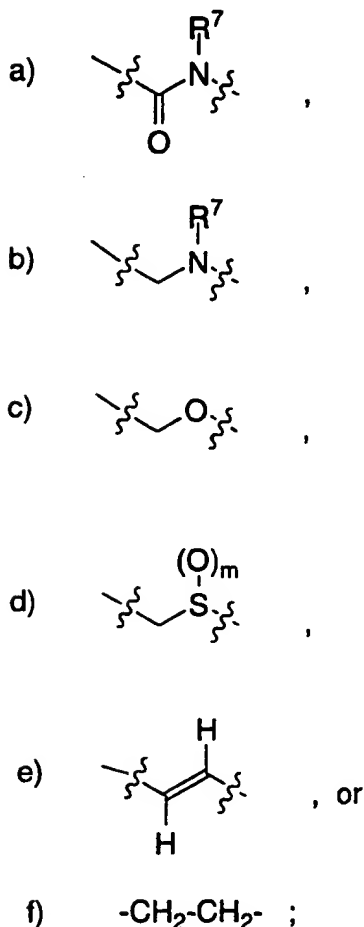
wherein:

- 424 -

V is CH_2 , O, S, HN, or R^7N ;

5 R^2 , R^3 , R^4 and R^5 are independently the side chains of naturally occurring amino acids, including their oxidized forms which may be methionine sulfoxide or methionine sulfone, or in the alternative may be substituted or unsubstituted aliphatic, aromatic or heteroaromatic groups, such as allyl, cyclohexyl, phenyl, pyridyl, imidazolyl or saturated chains of 2 to 8 carbon atoms which may be branched or
10 unbranched, wherein the aliphatic substituents may be substituted with an aromatic or heteroaromatic ring;

X-Y is

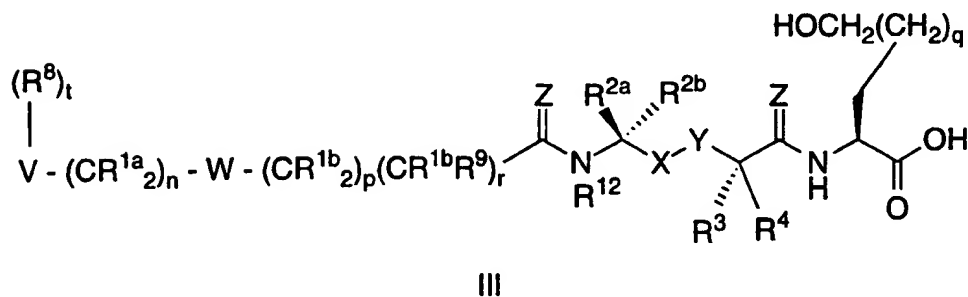
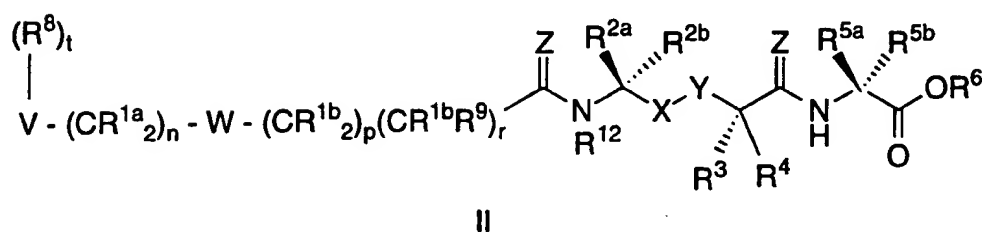
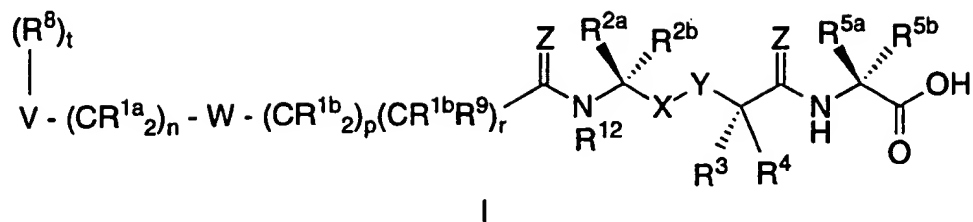


- 425 -

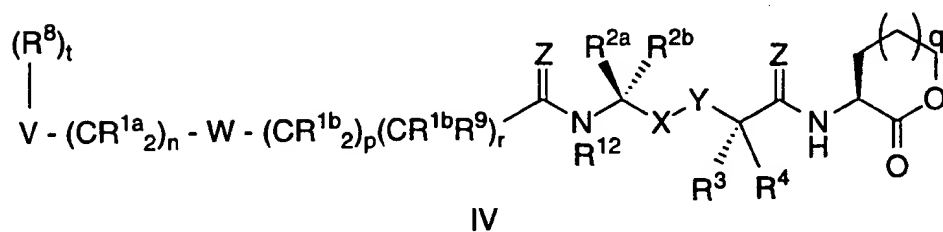
- 5 **R⁶ is** a substituted or unsubstituted aliphatic, aromatic or heteroaromatic group such as saturated chains of 1 to 8 carbon atoms, which may be branched or unbranched, wherein the aliphatic substituent may be substituted with an aromatic or heteroaromatic ring;
- 10 **R⁷ is** an alkyl group, wherein the alkyl group comprises straight chain or branched chain hydrocarbons of 1 to 6 carbon atoms, which may be substituted with an aromatic or heteroaromatic group;
- 15 **Z is** H₂ or O;
 m is 0, 1 or 2;
 n is 0, 1 or 2; and
 o is 0, 1, 2 or 3;

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s)



and



wherein:

R¹ᵃ is selected from:

5

- a) hydrogen,
- b) aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl,
(R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, or R¹⁰OC(O)-, and

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- 5 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R^{1b} is independently selected from:

- 10 a) hydrogen,
 b) unsubstituted or substituted aryl, cycloalkyl, alkenyl, alkynyl, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, or R¹⁰OC(O)-, and
 c) C₁-C₆ alkyl unsubstituted or substituted by unsubstituted or substituted aryl, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 15 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

provided that R^{1b} is not R¹⁰C(O)NR¹⁰- when R^{1a} is alkenyl, V is hydrogen and X-Y is -C(O)NR^{7a}-;

20 R^{2a} and R^{2b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or
 25 ii) methionine sulfone,
 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group, wherein the substituent is selected from F, Cl, Br, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 30 -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

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R^{2a} and R^{2b} are combined to form $-(CH_2)_s-$;

R³ and R⁴ are independently selected from:

- 5 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally
 occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
10 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀
 alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-,
15 N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
 and
 d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and
 C₃-C₁₀ cycloalkyl; or

20

R³ and R⁴ are combined to form $-(CH_2)_s-$;

R^{5a} and R^{5b} independently selected from:

- 25 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally
 occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
30 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀
 alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and

- 429 -

d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

5 R_{5a} and R_{5b} are combined to form - (CH₂)_s - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

R⁶ is

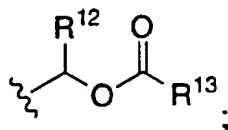
10

a) substituted or unsubstituted C₁-C₈ alkyl, wherein the substituent on the alkyl is selected from:

- 1) aryl,
- 2) heterocycle,
- 3) -N(R¹¹)₂,
- 4) -OR¹⁰, or

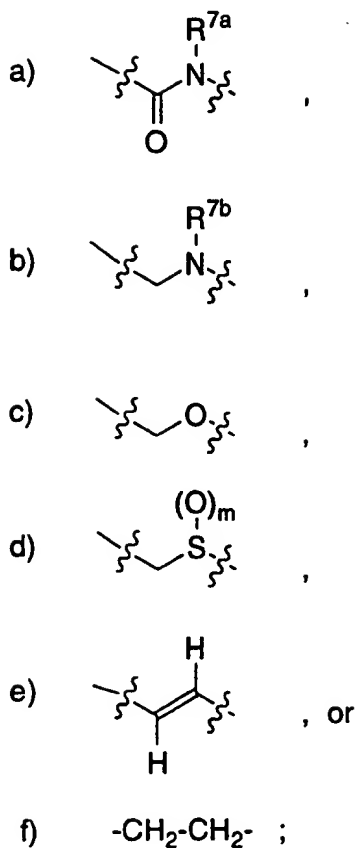
15

b)



- 430 -

X-Y is

R^{7a} is selected from

- 5 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocyclic,
 d) unsubstituted or substituted cycloalkyl, and
 e) C₁-C₆ alkyl substituted with hydrogen or an
 10 unsubstituted or substituted group selected from aryl,
 heterocyclic and cycloalkyl;

R^{7b} is selected from

- a) hydrogen,
 15 b) unsubstituted or substituted aryl,

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- 5 c) unsubstituted or substituted heterocyclic,
d) unsubstituted or substituted cycloalkyl,
e) C₁-C₆ alkyl substituted with hydrogen or an
unsubstituted or substituted group selected from aryl,
heterocyclic and cycloalkyl,
f) a carbonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocyclic,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
an unsubstituted or substituted group selected from aryl,
heterocyclic and cycloalkyl, and
10 g) a sulfonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocyclic,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or
an unsubstituted or substituted group selected from aryl,
heterocyclic and cycloalkyl;
15

R⁸ is independently selected from:

- a) hydrogen,
b) aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl,
20 perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-,
R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
R¹¹OC(O)NR¹⁰-, and
c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
25 heterocyclic, cycloalkyl, alkenyl, alkynyl,
perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-,
R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NH-;

30 R⁹ is selected from:

hydrogen, C₁-C₆ alkyl, R¹⁰O-, R¹¹S(O)_m-,
R¹⁰C(O)NR¹⁰-, CN, NO₂, N₃, -N(R¹⁰)₂, and
R¹¹OC(O)NR¹⁰-;

- 432 -

provided that R^9 is not $R^{10}C(O)NR^{10}$ - when R^{1a} is alkenyl, V is hydrogen and X-Y is $-C(O)NR^{7a}$ -;

5 R^{10} is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R^{11} is independently selected from C₁-C₆ alkyl and aryl;

10 R^{12} is independently selected from hydrogen and C₁-C₆ alkyl;

R^{13} is C₁-C₆ alkyl;

V is selected from:
15 a) aryl;
b) heterocycle; or
c) hydrogen;

20 W is $-S(O)_m-$, $-O-$, $-NHC(O)-$, $-C(O)NH-$, $-NHSO_2-$, $-SO_2NH-$, $-N(R^{7a})-$ or $-N[C(O)R^{7a}]$ -;

Z is independently H₂ or O;

m is 0, 1 or 2;
25 n is 0, 1, 2, 3 or 4, provided that $n \neq 0$ when V is hydrogen and W is

$-S(O)_m-$;

p is 0, 1, 2, 3 or 4, provided that $p \neq 0$ when R^9 is not hydrogen or C₁-C₆ lower alkyl ;

30 q is 0, 1 or 2;

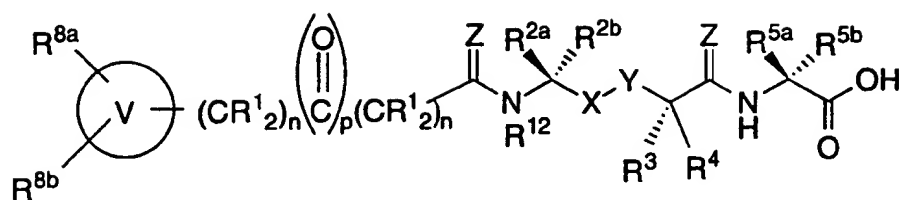
r is 0 or 1;

s is 4 or 5; and

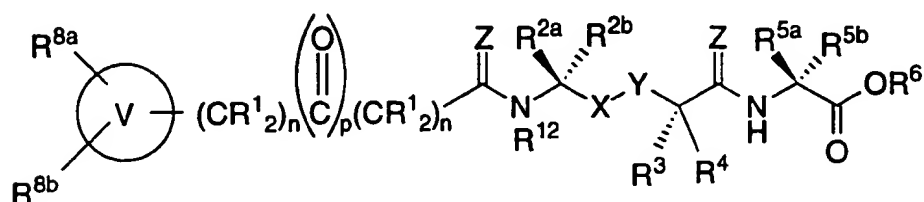
t is 0, 1 or 2, provided that $t = 0$ when V is hydrogen;

- 433 -

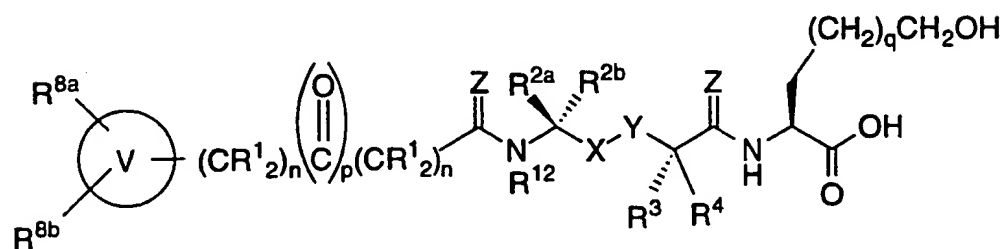
t)



I

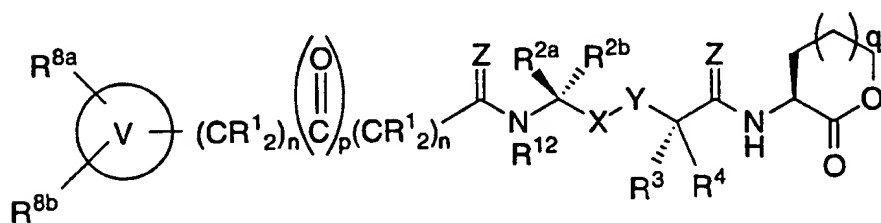


II



III

and



IV

wherein:

5 R1 is hydrogen, C1-C6 alkyl or aryl;

R2a and R2b are independently selected from:

- 434 -

- a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group, wherein the substituent is selected from F, Cl, Br, NO₂, R⁹O-, R¹⁰S(O)_m-, R⁹C(O)NR⁹-, CN, (R⁹)₂N-C(NR⁹)-, R⁹C(O)-, R⁹OC(O)-, N₃, -N(R⁹)₂, R¹⁰OC(O)NR⁹- and C₁-C₂₀ alkyl, and
d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

R_{2a} and R_{2b} are combined to form - (CH₂)_s - ;

R₃ and R₄ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group, wherein the substituent is selected from F, Cl, Br, NO₂, R⁹O-, R¹⁰S(O)_m-, R⁹C(O)NR⁹-, CN, (R⁹)₂N-C(NR⁹)-, R⁹C(O)-, R⁹OC(O)-, N₃, -N(R⁹)₂, R¹⁰OC(O)NR⁹- and C₁-C₂₀ alkyl, and
d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

R₃ and R₄ are combined to form - (CH₂)_s - ;

- 435 -

R^{5a} and R^{5b} are independently selected from:

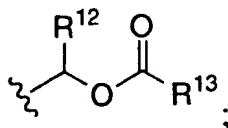
- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - i) methionine sulfoxide, or
 - ii) methionine sulfone,
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,

wherein the substituent is selected from F, Cl, Br, NO₂, R⁹O-, R¹⁰S(O)_m-, R⁹C(O)NR⁹-, CN, (R⁹)₂N-C(NR⁹)-, R⁹C(O)-, R⁹OC(O)-, N₃, -N(R⁹)₂, R¹⁰OC(O)NR⁹- and C₁-C₂₀ alkyl, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

R^{5a} and R^{5b} are combined to form - (CH₂)_s - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR⁹)- ;

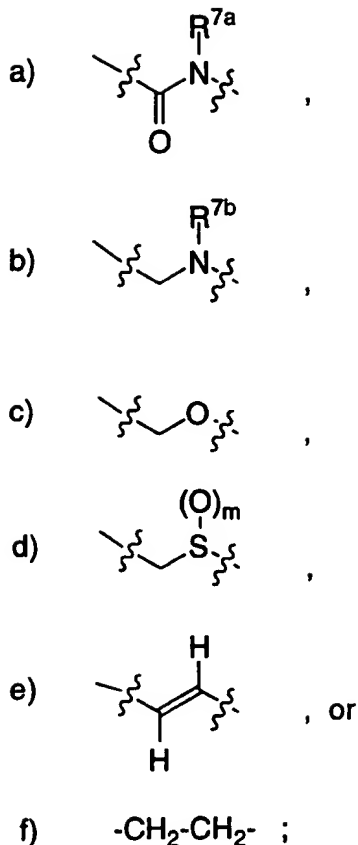
R⁶ is

- a) substituted or unsubstituted C₁-C₈ alkyl, wherein the substituent on the alkyl is selected from:
 - 1) aryl,
 - 2) heterocycle,
 - 3) -N(R¹⁰)₂,
 - 4) -OR⁹, or
- b)



- 436 -

X-Y is

R^{7a} is selected from

5

- a) hydrogen,
 - b) unsubstituted or substituted aryl,
 - c) unsubstituted or substituted heterocycle,
 - d) unsubstituted or substituted cycloalkyl, and
 - e) C₁-C₆ alkyl substituted with hydrogen or an
- 10 unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl;

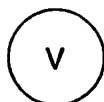
R^{7b} is selected from

15

- a) hydrogen,
- b) unsubstituted or substituted aryl,
- c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted cycloalkyl,

- 437 -

- e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl,
- 5 f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl, and
- 10 g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl;
- 15 R^{8a} and R^{8b} are independently selected from:
hydrogen, F, Cl, Br, NO₂, R¹¹O-, R¹⁰S(O)_m-, CN, R⁹C(O)NR⁹-, (R⁹)₂N-C(NR⁹)-, R⁹C(O)-, R⁹OC(O)-, N₃, -N(R⁹)₂, R¹⁰OC(O)NR⁹-, C₁-C₂₀ alkyl, aryl, heterocycle or C₁-C₂₀ alkyl substituted with aryl or
- 20 heterocycle;
- R⁹ is independently selected from hydrogen, C₁-C₆ alkyl and aryl;
- R¹⁰ is independently selected from C₁-C₆ alkyl and aryl;
- 25 R¹¹ is independently selected from hydrogen, C₁-C₆ alkyl and aryl, provided R¹¹ is C₁-C₆ alkyl when n is 0;
- R¹² is independently hydrogen or C₁-C₆ alkyl;
- 30 R¹³ is C₁-C₆ alkyl;



is aryl or 1,2,3,4-tetrahydronaphthyl;

- 438 -

Z is independently H₂ or O;

m is 0, 1 or 2;

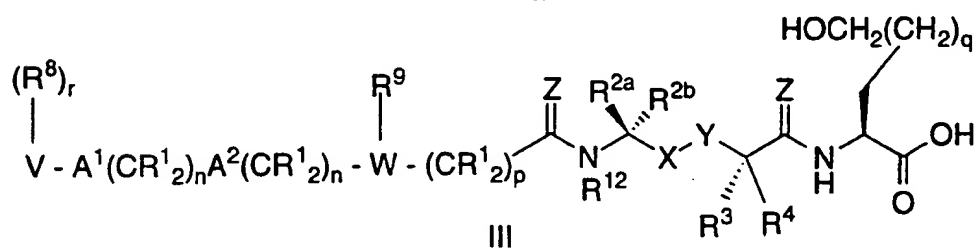
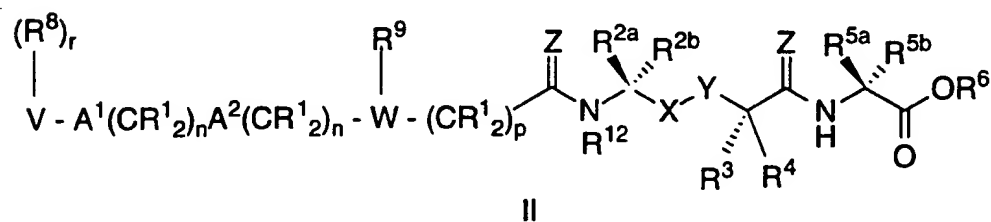
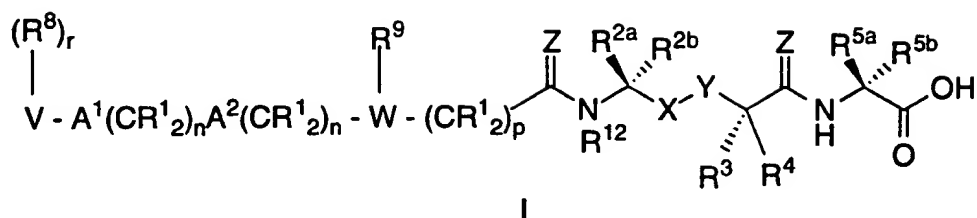
5 n is independently 0 to 4;

p is 0 or 1;

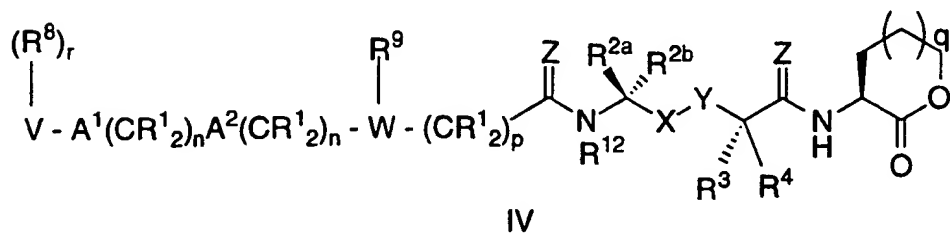
q is 0, 1 or 2; and

s is 4 or 5;

10 u)



or



- 439 -

wherein:

R¹ is independently selected from:

- 5 a) hydrogen,
 b) aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl,
 R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 heterocyclic, cycloalkyl, alkenyl, alkynyl, R¹⁰O-,
10 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-,
 R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-;
- R^{2a} and R^{2b} are independently selected from:
- 15 a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally
 occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,
20 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀
 alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
 wherein the substituent is selected from F, Cl, Br,
 NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
25 -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and
 d) C₁-C₆ alkyl substituted with an unsubstituted or
 substituted group selected from aryl, heterocycle and
 C₃-C₁₀ cycloalkyl; or

30 R^{2a} and R^{2b} are combined to form - (CH₂)_s - ;

R³ and R⁴ are independently selected from:

- a) a side chain of a naturally occurring amino acid,

- 440 -

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

5 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group, wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, 10 N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and

d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

15

R³ and R⁴ are combined to form - (CH₂)_s - ;

R^{5a} and R^{5b} are independently selected from:

20 a) a side chain of a naturally occurring amino acid, b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

25 c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group, wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, 30 N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and

d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

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R5a and R5b are combined to form $-(CH_2)_s-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

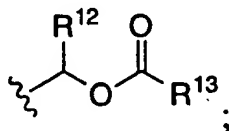
5 R⁶ is

a) substituted or unsubstituted C₁-C₈ alkyl, wherein the substituent on the alkyl is selected from:

- 1) aryl,
- 2) heterocycle,
- 3) -N(R¹¹)₂,
- 4) -OR¹⁰, or

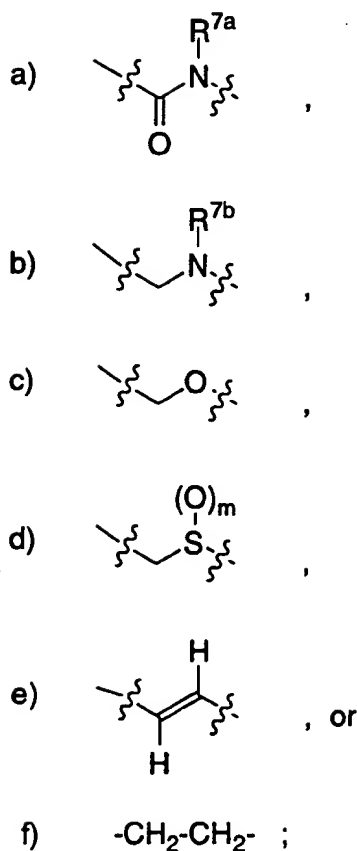
10

b)



- 442 -

X-Y is

R^{7a} is selected from

- 5 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocyclic,
 d) unsubstituted or substituted cycloalkyl, and
 e) C₁-C₆ alkyl substituted with hydrogen or an
 10 unsubstituted or substituted group selected from aryl,
 heterocyclic and cycloalkyl;

R^{7b} is selected from

- a) hydrogen,
 15 b) unsubstituted or substituted aryl,

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- 5 c) unsubstituted or substituted heterocyclic,
d) unsubstituted or substituted cycloalkyl,
e) C₁-C₆ alkyl substituted with hydrogen or an
unsubstituted or substituted group selected from aryl,
heterocyclic and cycloalkyl,
f) a carbonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocyclic,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen
or an unsubstituted or substituted group selected from
10 aryl, heterocyclic and cycloalkyl, and
g) a sulfonyl group which is bonded to an unsubstituted
or substituted group selected from aryl, heterocyclic,
cycloalkyl and C₁-C₆ alkyl substituted with hydrogen
or an unsubstituted or substituted group selected from
15 aryl, heterocyclic and cycloalkyl;

R⁸ is independently selected from:

- 20 a) hydrogen,
b) aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl,
perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-,
R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
R¹¹OC(O)NR¹⁰-, and
c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
25 heterocyclic, cycloalkyl, alkenyl, alkynyl,
perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-,
R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NH-;

30 R⁹ is selected from:

- a) hydrogen,
b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-

- 444 -

C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and

5 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl and aryl;

10 R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

R¹² is independently selected from hydrogen and C₁-C₆ alkyl;

R¹³ is independently selected from C₁-C₆ alkyl;

15

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, O, -N(R¹⁰)-, -NR¹⁰C(O)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂- or S(O)_m;

20

V is selected from:

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- 25 d) C₁-C₂₀ alkyl wherein from 0 to 4 non-terminal carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl ;

30 provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m or a bond;

W is a heterocycle;

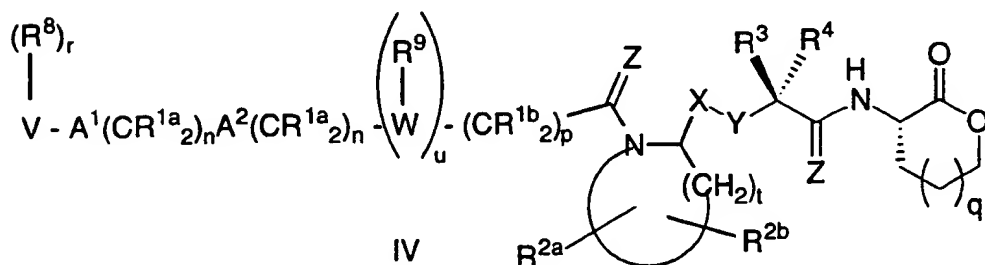
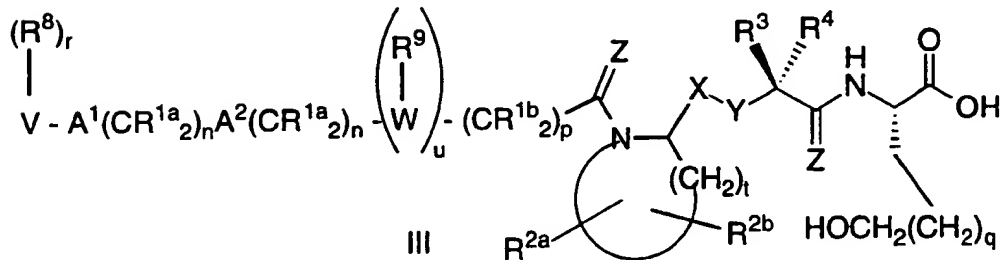
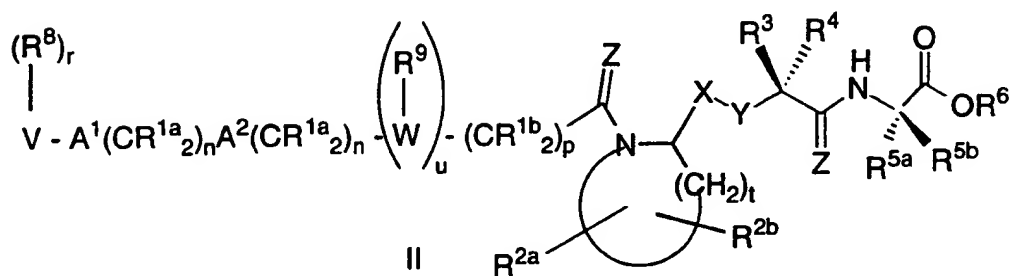
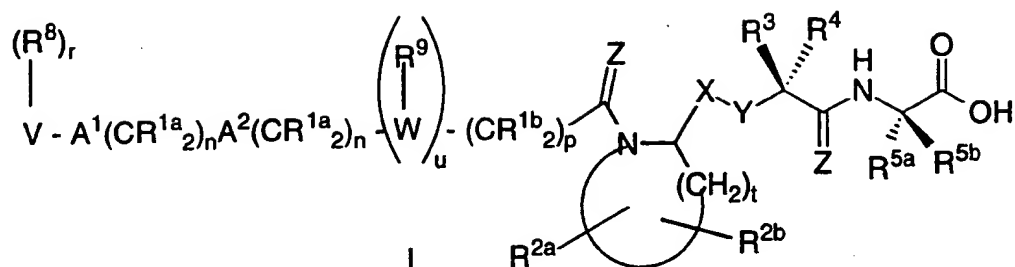
Z is independently H₂ or O;

- 445 -

- m is 0, 1 or 2;
- n is 0, 1, 2, 3 or 4;
- p is 0, 1, 2, 3 or 4;
- 5 q is 0, 1 or 2;
- r is 0 to 5, provided that r is 0 when V is hydrogen; and
- s is 4 or 5;

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v)



wherein:

R^{1a} and R^{1b} are independently selected from:

5

a) hydrogen,

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- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 5 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)-NR¹⁰-;
- 10

R^{2a} and R^{2b} are independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 15 c) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;
- 25

R³ and R⁴ are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
- 30 i) methionine sulfoxide, or
- ii) methionine sulfone,
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,

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wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1 - C_{20} alkyl, and

5

- d) C_1 - C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3 - C_{10} cycloalkyl; or

10 R^3 and R^4 are combined to form $-(CH_2)_s-$;

R^{5a} and R^{5b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
 b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 15 i) methionine sulfoxide, or
 ii) methionine sulfone,
 c) substituted or unsubstituted C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, C_3 - C_{10} cycloalkyl, aryl or heterocycle group,

20

wherein the substituent is selected from F, Cl, Br, CF_3 , $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1 - C_{20} alkyl, and

25

- d) C_1 - C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3 - C_{10} cycloalkyl; or

30 R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, $-NC(O)-$, and $-N(COR^{10})-$;

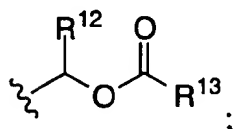
- 449 -

R⁶ is

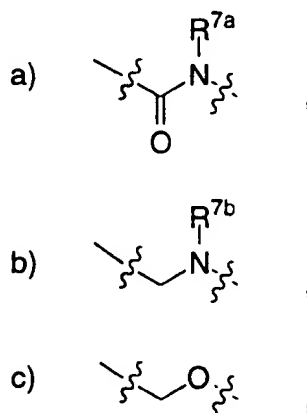
- a) substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₅-C₈ cycloalkyl, or substituted or unsubstituted cyclic amine, wherein the substituted alkyl, cycloalkyl or cyclic amine is substituted with 1 or 2 substituents independently selected from:

- 1) C₁-C₆ alkyl,
- 2) aryl,
- 3) heterocycle,
- 4) -N(R¹¹)₂,
- 5) -OR¹⁰, or

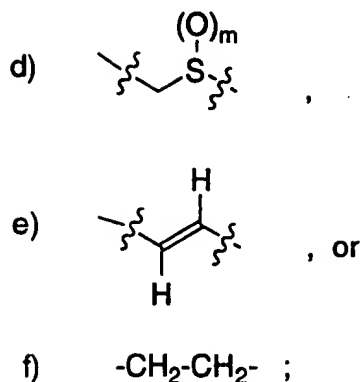
b)



15 X-Y is



- 450 -

R^{7a} is selected from

- 5 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted C₃-C₁₀ cycloalkyl, and
 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted
 10 or substituted group selected from aryl, heterocycle and
 C₃-C₁₀ cycloalkyl;

R^{7b} is selected from

- 15 a) hydrogen,
 b) unsubstituted or substituted aryl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
 e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted
 or substituted group selected from aryl, heterocycle and
 C₃-C₁₀ cycloalkyl,
 20 f) a carbonyl group which is bonded to an unsubstituted or
 substituted group selected from aryl, heterocycle, C₃-C₁₀
 cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an
 unsubstituted or substituted group selected from aryl,
 heterocycle and C₃-C₁₀ cycloalkyl, and
 25 g) a sulfonyl group which is bonded to an unsubstituted or
 substituted group selected from aryl, heterocycle, C₃-C₁₀

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cycloalkyl and C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

5 R₈ is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 10 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;
- 15

R₉ is selected from:

- a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 20 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;
- 25

R₁₀ is independently selected from H, C₁-C₆ alkyl, benzyl, substituted aryl and C₁-C₆ alkyl substituted with substituted aryl;

30

R₁₁ is independently selected from C₁-C₆ alkyl and aryl;

R₁₂ is hydrogen or C₁-C₆ alkyl;

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R¹³ is C₁-C₆ alkyl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
-C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-,
5 -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

V is selected from:

- a) hydrogen,
 - b) heterocycle,
 - 10 c) aryl,
 - d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are
replaced with a heteroatom selected from O, S, and N,
and
 - e) C₂-C₂₀ alkenyl ,
- 15 provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen
if A¹ is a bond, n is 0 and A² is S(O)_m;

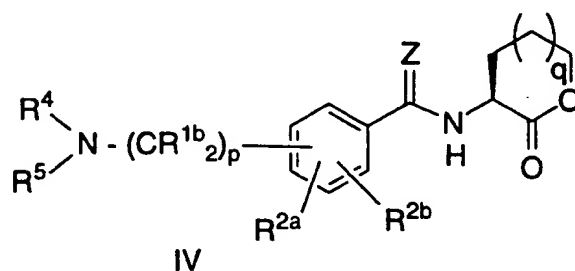
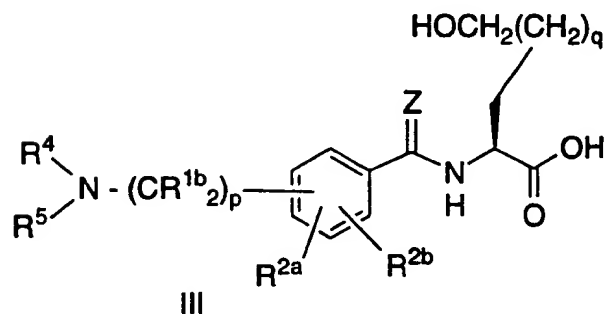
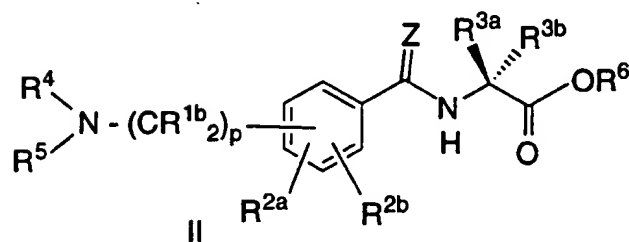
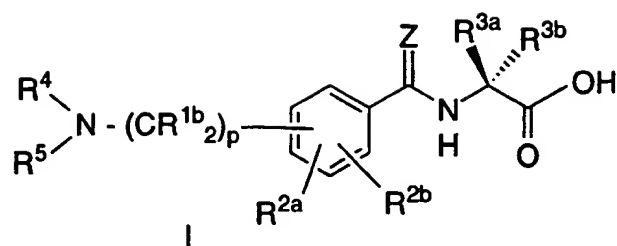
W is a heterocycle;

20 Z is independently H₂ or O;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
25 q is 0, 1 or 2;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 4 or 5;
t is 3, 4 or 5; and
u is 0 or 1;
30

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w)



wherein:

R^{1a} and R^{1b} are independently selected from:

- 5 a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, R¹⁰O-,
R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
(R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
-N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,

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- 5 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)-NR¹⁰-;

R^{2a} and R^{2b} are independently selected from:

- 10 a) hydrogen,
b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
15 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃- C₁₀ cycloalkyl;

20

R^{3a} and R^{3b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
25 i) methionine sulfoxide, or
ii) methionine sulfone, and
c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocyclic group,
wherein the substituent is selected from F, Cl, Br,
30 N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl, and

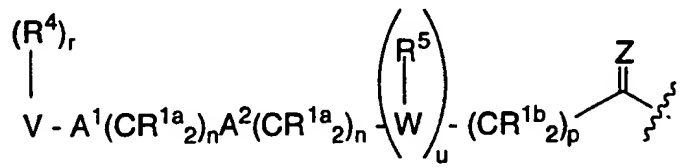
- 455 -

- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl; or

- 5 R^{3a} and R^{3b} are combined to form -(CH₂)_s - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)- ;

R⁴ and R⁵ are independently selected from:

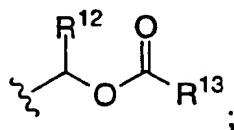
- 10 a) hydrogen, and
b)



R⁶ is

- 15 a) substituted or unsubstituted C₁-C₈ alkyl or substituted or unsubstituted C₅-C₈ cycloalkyl, wherein the substituent on the alkyl is selected from:
- 20 1) aryl,
2) heterocycle,
3) -N(R¹¹)₂,
4) -OR¹⁰, or

b)



- 25 R⁷ is independently selected from:

- a) hydrogen,
b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 30

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- 5 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

R⁸ is selected from:

- 10 a) hydrogen,
b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
15 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

20

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

R¹² is independently selected from hydrogen and C₁-C₆ alkyl;

25 R¹³ is independently selected from C₁-C₆ alkyl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

30

V is selected from:

- a) hydrogen,
b) heterocycle,
c) aryl,

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- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl,
- 5 provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

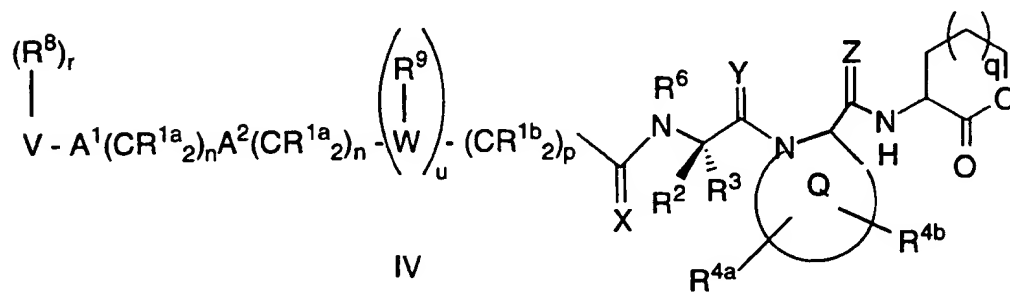
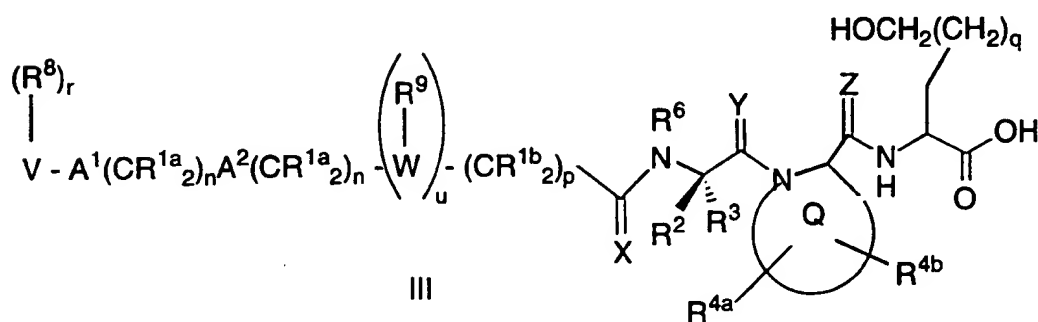
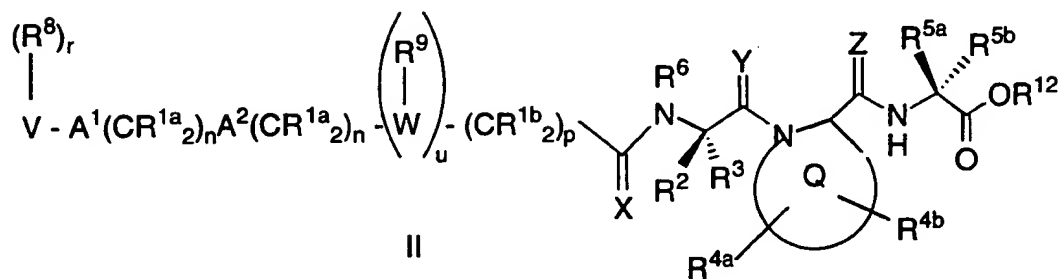
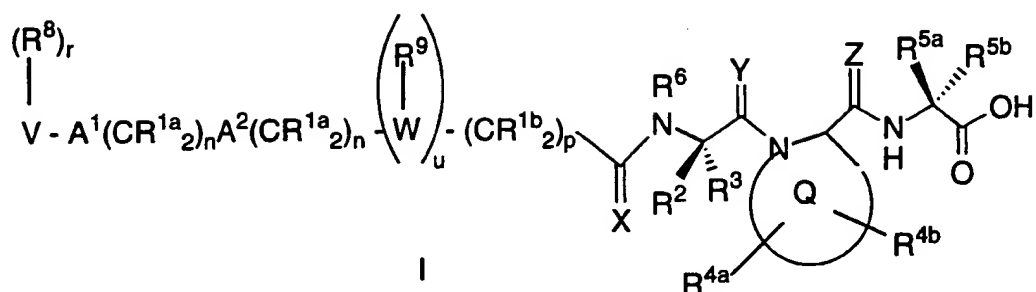
W is a heterocycle;

- 10 Z is independently H₂ or O;

- m is 0, 1 or 2;
- n is 0, 1, 2, 3 or 4;
- p is 0, 1, 2, 3 or 4;
- 15 q is 0, 1 or 2;
- r is 0 to 5, provided that r is 0 when V is hydrogen;
- s is 4 or 5; and
- u is 0 or 1;

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x)



wherein:

5 R¹ᵃ and R¹ᵇ are independently selected from:

a) hydrogen,

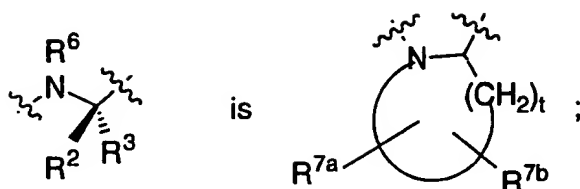
- 459 -

- b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , NO_2 , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,
- 5 c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclic, cycloalkyl, alkenyl, alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$;
- 10 R^2 and R^3 are independently selected from:
- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
- 15 i) methionine sulfoxide, or
- ii) methionine sulfone, and
- c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclic group,
- 20 wherein the substituent is selected from F , Cl , Br , $N(R^{10})_2$, NO_2 , $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN , $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}-$ and C_1-C_{20} alkyl, and
- d) C_1-C_6 alkyl substituted with an unsubstituted or
- 25 substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form $-(CH_2)_5-$; or

30 R^2 or R^3 are combined with R^6 to form a ring such that

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R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

- a) hydrogen,
- 5 b) C₁-C₆ alkyl unsubstituted or substituted by alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) aryl, heterocycle, cycloalkyl, alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
10 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;

15

R^{5a} and R^{5b} are independently selected from:

- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 - 20 i) methionine sulfoxide, or
 - ii) methionine sulfone,
- c) substituted or unsubstituted C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₃-C₁₀ cycloalkyl, aryl or heterocycle group,
 wherein the substituent is selected from F, Cl, Br,
 25 N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C₁-C₂₀ alkyl,
- d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and
 30 C₃-C₁₀ cycloalkyl; or

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R5a and R5b are combined to form $-(CH_2)_s-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m, -NC(O)-, and -N(COR¹⁰)-;

5 R⁶ is independently selected from hydrogen or C₁-C₆ alkyl;

R⁸ is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, cycloalkyl, alkenyl, alkynyl,
10 perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,
R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-,
R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
15 heterocycle, cycloalkyl, alkenyl, alkynyl, perfluoroalkyl, F,
Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-
C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
20 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-
(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or
R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl,
25 F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
(R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃,
-N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

30 R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

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R¹² is

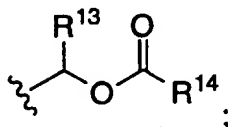
- a) substituted or unsubstituted C₁-C₈ alkyl or substituted or unsubstituted C₅-C₈ cycloalkyl, wherein the substituent on the alkyl or cycloalkyl is selected from:

5

- 1) aryl,
- 2) heterocycle,
- 3) -N(R¹¹)₂,
- 4) -OR¹⁰, or

b)

10



R¹³ is independently selected from hydrogen and C₁-C₆ alkyl;

R¹⁴ is independently selected from C₁-C₆ alkyl;

15

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

20 Q is a substituted or unsubstituted nitrogen-containing C₄-C₉ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C₅-C₇ saturated ring or a heterocycle;

V is selected from:

25

- a) hydrogen,
- b) heterocycle,
- c) aryl,
- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N,

30

- e) C₂-C₂₀ alkenyl,

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provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle;

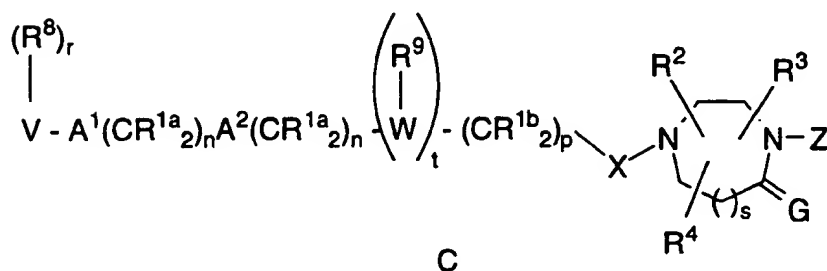
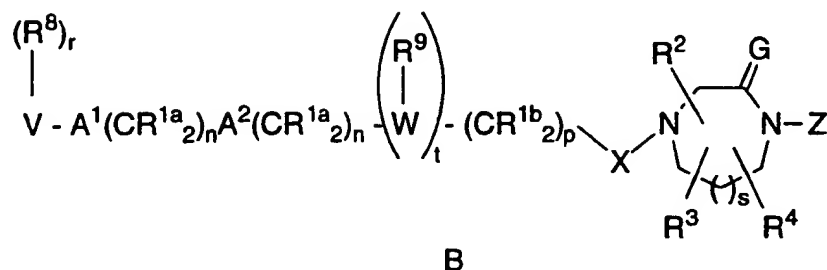
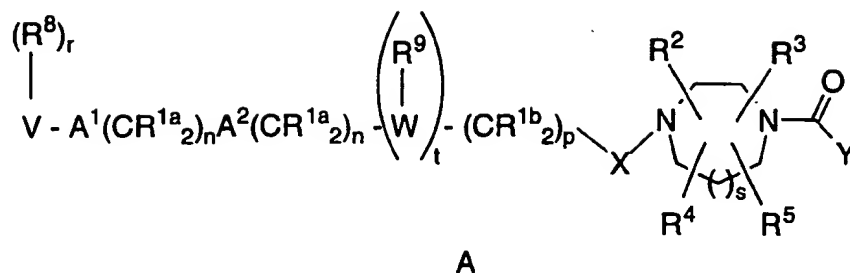
5

X, Y and Z are independently H₂ or O;

	m is	0, 1 or 2;
	n is	0, 1, 2, 3 or 4;
10	p is	0, 1, 2, 3 or 4;
	q is	0, 1 or 2;
	r is	0 to 5, provided that r is 0 when V is hydrogen;
	s is	4 or 5;
	t is	3, 4 or 5; and
15	u is	0 or 1;

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y)



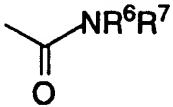
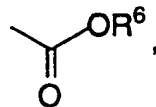
wherein:

- 5 R^{1a} and R^{1b} are independently selected from:
- a) hydrogen,
 - b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 - c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN,
- 10

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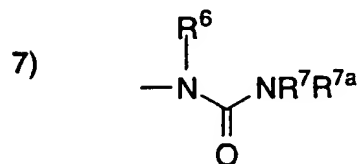
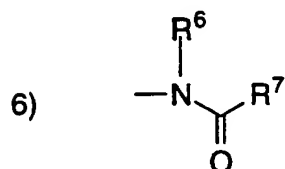
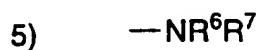
$(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 ,
 $-N(R^{10})_2$, or $R^{11}OC(O)-NR^{10}-$;

R^2 and R^3 are independently selected from: H; unsubstituted or
 5 substituted C₁₋₈ alkyl, unsubstituted or substituted C₂₋₈ alkenyl,
 unsubstituted or substituted C₂₋₈ alkynyl, unsubstituted or substituted aryl,

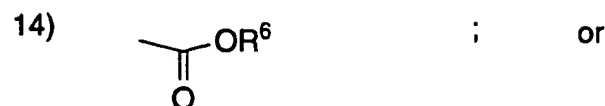
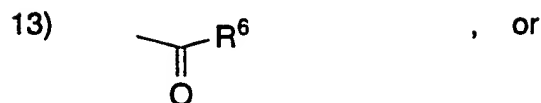
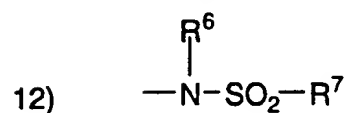
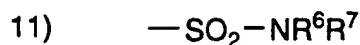
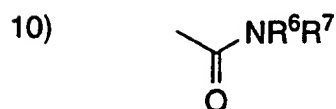
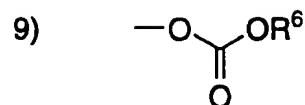
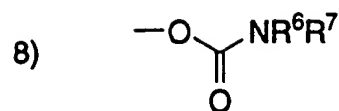
unsubstituted or substituted heterocycle,  or ,

wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) C₁₋₄ alkyl,
 - b) $(CH_2)_pOR^6$,
 - c) $(CH_2)_pNR^6R^7$,
 - d) halogen,
- 2) C₃₋₆ cycloalkyl,
- 3) OR^6 ,
- 4) SR^6 , $S(O)R^6$, SO_2R^6 ,



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5 R^2 and R^3 are attached to the same C atom and are combined to form $(\text{CH}_2)_u$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m , —NC(O)— , and $\text{—N(COR}^{10})\text{—}$;

R^4 is selected from H and CH_3 ;

10

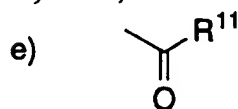
and any two of R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

15 R^6 , R^7 and R^{7a} are independently selected from: H; C1-4 alkyl, C3-6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C1-4 alkoxy,

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- b) aryl or heterocycle,
- c) halogen,
- d) HO,



- f) $-\text{SO}_2\text{R}^{11}$, or
- g) $\text{N}(\text{R}^{10})_2$; or

5

R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

10 R^8 is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, CN, NO₂, $\text{R}^{10}_2\text{N}-\text{C}(\text{NR}^{10})-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$, and
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NH}-$, CN, $\text{H}_2\text{N}-\text{C}(\text{NH})-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{10}\text{OC}(\text{O})\text{NH}-$;

15

20

R^9 is selected from:

- a) hydrogen,
- b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, CN, NO₂, $(\text{R}^{10})_2\text{N}-\text{C}(\text{NR}^{10})-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$, and
- c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{11}\text{S}(\text{O})_m-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, CN, $(\text{R}^{10})_2\text{N}-\text{C}(\text{NR}^{10})-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, N₃, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$;

25

30

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R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;

5 R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
-C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-,
-S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

10

G is H₂ or O;

V is selected from:

- 15 a) hydrogen,
b) heterocycle,
c) aryl,
d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are
replaced with a heteroatom selected from O, S, and N,
and
20 e) C₂-C₂₀ alkenyl,
provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen
if A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle;

25

X is -CH₂-, -C(=O)-, or -S(=O)_m-;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

30

- 1) C₁-4 alkyl, unsubstituted or substituted with:
a) C₁-4 alkoxy,
b) NR⁶R⁷,
c) C₃-6 cycloalkyl,
d) aryl or heterocycle,

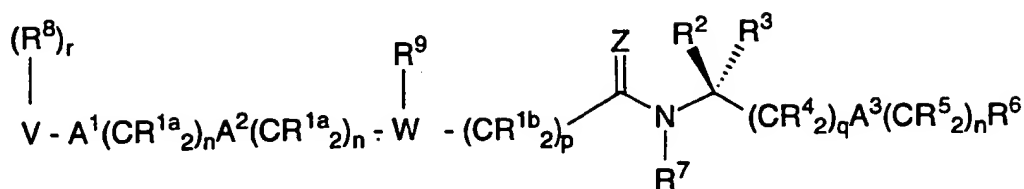
- 469 -

- 5
- 10
- 15 Z is
- 20
- 25
- 30
- e) HO,
 - f) $-S(O)_mR^6$, or
 - g) $-C(O)NR^6R^7$,
 - 2) aryl or heterocycle,
 - 3) halogen,
 - 4) OR^6 ,
 - 5) NR^6R^7 ,
 - 6) CN,
 - 7) NO_2 ,
 - 8) CF_3 ;
 - 9) $-S(O)_mR^6$,
 - 10) $-C(O)NR^6R^7$, or
 - 11) C3-C6 cycloalkyl;
- aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:
- 1) C1-4 alkyl, unsubstituted or substituted with:
 - a) C1-4 alkoxy,
 - b) NR^6R^7 ,
 - c) C3-6 cycloalkyl,
 - d) aryl or heterocycle,
 - e) HO,
 - f) $-S(O)_mR^6$, or
 - g) $-C(O)NR^6R^7$,
 - 2) aryl or heterocycle,
 - 3) halogen,
 - 4) OR^6 ,
 - 5) NR^6R^7 ,
 - 6) CN,
 - 7) NO_2 ,
 - 8) CF_3 ;
 - 9) $-S(O)_mR^6$,
 - 10) $-C(O)NR^6R^7$, or

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11) C3-C6 cycloalkyl;

- m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 5 p is 0, 1, 2, 3 or 4;
 r is 0 to 5, provided that r is 0 when V is hydrogen;
 s is 0 or 1;
 t is 0 or 1; and
 u is 4 or 5;
 10 z)



I

wherein:

R^{1a} is independently selected from:

- 15 a) hydrogen,
 b) aryl, heterocycle, C3-C10 cycloalkyl, C2-C20 alkenyl, C2-C20 alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
 20 c) C1-C6 alkyl unsubstituted or substituted by aryl, heterocyclic, C3-C10 cycloalkyl, C2-C20 alkenyl, C2-C20 alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)-NR¹⁰-;
 25

R^{1b} is independently selected from:

- a) hydrogen,

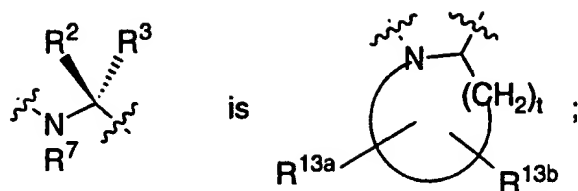
- 471 -

- b) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C3-C10 cycloalkyl, C2-C20 alkenyl, C2-C20 alkynyl, R¹⁰O-, R¹¹S(O)_m-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃ or -N(R¹⁰)₂,
- 5 c) C1-C6 alkyl unsubstituted or substituted by substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic, C3-C10 cycloalkyl, C2-C20 alkenyl, C2-C20 alkynyl, R¹⁰O-, R¹¹S(O)_m-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃ or -N(R¹⁰)₂;
- 10 R² and R³ are independently selected from:
- a) a side chain of a naturally occurring amino acid,
- b) an oxidized form of a side chain of a naturally occurring amino acid which is:
- 15 i) methionine sulfoxide, or
- ii) methionine sulfone, and
- c) substituted or unsubstituted C1-C20 alkyl, substituted or unsubstituted C2-C20 alkenyl, substituted or unsubstituted C3-C10 cycloalkyl, substituted or unsubstituted aryl or
- 20 substituted or unsubstituted heterocyclic group,
- wherein the substituent is selected from F, Cl, Br, N(R¹⁰)₂, NO₂, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, R¹¹OC(O)NR¹⁰- and C1-C20 alkyl,
- 25 and
- d) C1-C6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C3-C10 cycloalkyl; or

30 R² and R³ are combined to form - (CH₂)_s - ; or

R² or R³ are combined with R⁷ to form a ring such that

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R⁴, R⁵, R^{13a} and R^{13b} are independently selected from:

- 5 a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₂₀ alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, N₃, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 10 d) C₁-C₆ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C₃-C₁₀ cycloalkyl;
- 15

R⁶ is selected from:

- 20 a) hydrogen,
- b) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₁-C₂₀ perfluoroalkyl, allyloxy, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, (R¹²)₂NC(O)- or R¹¹OC(O)NR¹⁰-, and
- 25 c) C₁-C₆ alkyl unsubstituted or substituted by substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₂-C₂₀ perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;
- 30

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R⁷ is independently selected from

- a) hydrogen,
- b) unsubstituted or substituted aryl,
- 5 c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted C₃-C₁₀ cycloalkyl, and
- e) C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C₃-C₁₀ cycloalkyl;

10

R⁸ is selected from:

- a) hydrogen,
- b) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₁-C₂₀ perfluoroalkyl, allyloxy, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, -S(O)₂NR¹⁰₂, CN, NO₂, R¹⁰₂N-C(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 15 c) C₁-C₆ alkyl unsubstituted or substituted by substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₂-C₂₀ perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NH-, CN, H₂N-C(NH)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹⁰OC(O)NH-;

20

R⁹ is selected from:

- a) hydrogen,
- b) C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₂-C₂₀ perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C-(NR¹⁰)-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
- 25 c) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₂₀ perfluoroalkyl, F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-,

30

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$R^{10}C(O)NR^{10}$ -, CN, $(R^{10})_2N-C(NR^{10})$ -, $R^{10}C(O)$ -,
 $R^{10}OC(O)$ -, N_3 , $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$ -;

5 R^{10} is independently selected from hydrogen, C1-C6 alkyl, benzyl and aryl;

R^{11} is independently selected from C1-C6 alkyl and aryl;

10 R^{12} is independently selected from hydrogen, C1-C6 alkyl and aryl, or $(R^{12})_2$ forms - $(CH_2)_s$ - ;

15 A^1 , A^2 and A^3 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$, $-C(O)-$, $-C(O)NR^7$ -, $-NR^7C(O)-$, O, $-N(R^7)-$, $-S(O)_2N(R^7)-$, $-N(R^7)S(O)_2-$, or $S(O)_m$;

15

V is selected from:

- 20 a) hydrogen,
b) heterocycle,
c) aryl,
d) C1-C20 alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C2-C20 alkenyl,

25 provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

30 Z is independently H2 or O;

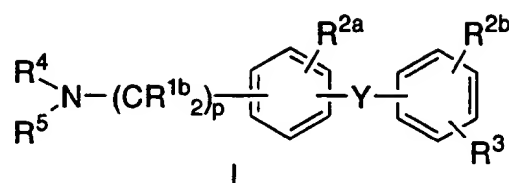
m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 0, 1, 2, 3 or 4;

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r is 0 to 5, provided that r is 0 when V is hydrogen;
 s is 4 or 5; and
 t is 3, 4 or 5;

5 or

aa)



10 wherein:

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-,
- c) C₁-C₆ alkyl unsubstituted or substituted by unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)-NR⁸-;

R^{2a}, R^{2b} and R³ are independently selected from:

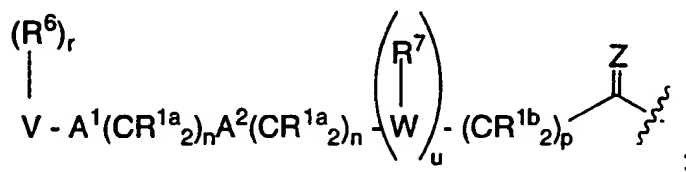
- a) hydrogen,
- b) C₁-C₆ alkyl unsubstituted or substituted by C₂-C₆ alkenyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, N₃, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

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- 5 c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted cycloalkyl, alkenyl, R^8O- , $R^9S(O)_m-$, $R^8C(O)NR^8-$, CN, NO_2 , $(R^8)_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3 , $-N(R^8)_2$, halogen or $R^9OC(O)NR^8-$, and
- 10 d) C1-C6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C3-C10 cycloalkyl;

15 R^4 and R^5 are independently selected from:

- a) hydrogen, and
- b)



15

R^6 is independently selected from:

- a) hydrogen,
- 20 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C3-C6 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl, Br, R^8O- , $R^9S(O)_m-$, $R^8C(O)NR^8-$, CN, NO_2 , $R^8_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3 , $-N(R^8)_2$, or $R^9OC(O)NR^8-$, and
- 25 c) C1-C6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C3-C6 cycloalkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 perfluoroalkyl, F, Cl, Br, R^8O- , $R^9S(O)_m-$, $R^8C(O)NH-$, CN, $H_2N-C(NH)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3 , $-N(R^8)_2$, or $R^8OC(O)NH-$;

30

R^7 is selected from:

- a) hydrogen,

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- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C-(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
- 5 c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-;
- 10 R⁸ is independently selected from hydrogen, C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ aralkyl and substituted or unsubstituted aryl;
- R⁹ is independently selected from C₁-C₆ alkyl and aryl;
- 15 R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ aralkyl and substituted or unsubstituted aryl;
- 20 A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR⁸-, -NR⁸C(O)-, O, -N(R⁸)-, -S(O)₂N(R⁸)-, -N(R⁸)S(O)₂-, or S(O)_m;
- V is selected from:
- 25 a) hydrogen,
 b) heterocycle,
 c) aryl,
 d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N,
 30 and
 e) C₂-C₂₀ alkenyl,
- provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

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W is a heterocycle;

Y is selected from: a bond, -C(R¹⁰)=C(R¹⁰)-, -C≡C-, -C(O)-, -C(R¹⁰)-
 2-, -C(OR¹⁰)R¹⁰-, -CN(R¹⁰)₂R¹⁰-, -OC(R¹⁰)₂-, -NR¹⁰C(R¹⁰)₂-,
 5 -C(R¹⁰)₂O-, -C(R¹⁰)₂NR¹⁰-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O,
 -NC(O)R¹⁰-, -NC(O)OR¹⁰-, -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or
 S(O)_m;

Z is H₂ or O;

10

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

r is 0 to 5, provided that r is 0 when V is hydrogen; and

15

u is 0 or 1;

or a pharmaceutically acceptable salt thereof.

6. The method according to Claim 5 wherein the
 20 protein substrate competitive inhibitor is selected from:

5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-n-propyl-
 3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,

25 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-methyl-
 3,4-E-octenoyl-homserine, and the corresponding homoserine lactone,

5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-ethyl-3,4-
 E-octenoyl-homserine, and the corresponding homoserine lactone,

30

5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-i-propyl-
 3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,

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- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-n-butyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-s-butyl-
5 3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-t-butyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 10 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-cyclohexyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-
15 cyclopentyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-benzyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
20 5(S)-[2(R)-amino-3-mercaptopropylamino]-6-methyl-2(R)-i-propyl-3,4-E-octenoyl-homoserine, and the corresponding homoserine lactone,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-i-propyl-
25 3,4-E-octenoyl-methionine, and the corresponding methyl ester,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-n-butyl-3,4-E-octenoyl-methionine, and the corresponding methyl ester,
- 30 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-benzyl-3,4-E-octenoyl-methionine, and the corresponding methyl ester,
- 5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-n-propyl-octanoyl-homoserine, and the corresponding homoserine lactone,

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5(S)-[2(R)-amino-3-mercaptopropylamino]-6(S)-methyl-2(R)-benzyl-octanoyl-homoserine, and the corresponding homoserine lactone,

5 N-(3-phenyl-2(S)-(mercaptopropionylamino)prop-1-yl)isoleucyl-methionine,

N-(2(R)-amino-3-mercaptopropyl)isoleucyl-phenylalanyl-methionine,

10 N-(3-mercaptopropyl)isoleucyl-phenylalanyl-methionine,

N-(3-mercaptopropyl)valyl-isoleucyl-methionine,

N-(2(R)-amino-3-mercaptopropyl)valyl-isoleucyl-methionine,

15

N-(3-methyl-2(S)-(cysteinylamino)but-1-yl)phenylalanyl-methionine,

N-(3-methyl-2(S)-(mercaptopropionylamino)but-1-yl)-phenylalanyl-methionine,

20

N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)methylpentyl]-phenylalanyl-methionine,

25 N-[2(S)-(3-mercaptopropylamino)-3(S)methylpentyl]-phenylalanyl-methionine,

N-(2(R)-amino-3-mercaptopropyl)isoleucyl-phenylalanyl-(methionine sulfone),

30 N-(2(R)-amino-3-mercaptopropyl)isoleucyl-(p-iodophenylalanyl)-methionine,

N-[2(R)-(cysteinyl-isoleucylamino)-3(S)-methylpentyl]-methionine,

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N-[2(R)-(N'-(2(R)-amino-3-mercaptopropyl)-isoleucylamino)-3-phenylpropyl]methionine,

5 N-[2(R)-(N'-(2(R)-amino-3-mercaptopropyl)-isoleucylamino)-3(S)-methylpentyl]methionine,

N-(3-mercaptopropyl)valyl-isoleucyl-methionine methyl ester,

10 N-(2(R)-amino-3-mercaptopropyl)isoleucyl-phenylalanyl-methionine ethyl ester,

N-(2(R)-amino-3-mercaptopropyl)isoleucyl-phenylalanyl-methionine benzyl ester,

15 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-phenethylamide,

N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-benzylamide,

20 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-3-methylbutylamide,

N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-3-phenylpropylamide,

N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucyl-L-phenylalaninol,

25 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-N'-methylbenzylamide,

N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(4-methoxybenzyl)amide,

30 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2,4-dichlorobenzyl)amide,

N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(4-trifluoromethylbenzyl)amide,

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N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2,4-dichloro-phenethyl)amide,

5 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2-benzimidazol-ylmethyl)amide,

N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(1-indanyl)amide,

10 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2,4-dimethyl-benzyl)amide,

N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2,3-dichloro-benzyl)amide,

15 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(4-sulfamoyl-benzyl)amide,

20 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucineanilide,

N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2,4-dimethyl-phenyl)amide,

25 N-[2(R)-Amino-3-mercaptopropyl]-L-isoleucine-(2,3-dimethyl-phenyl)amide,

L-Cysteiny-L-isoleucine-phenethylamide,

30 N-[2(S)-[2(R)-Amino-3-mercaptopropylamino]-3-methylpentyl]-phenethylamide,

N-(2(R)-Amino-3-mercaptopropyl)-L-alaninebenzylamide,

N-Benzyl-[2(S)-2(R)-Amino-3-mercaptopropyl)-amino]butyramide,

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N-(2(R)-Amino-3-mercaptopropyl)-L-norleucinebenzylamide,

N-(2(R)-Amino-3-mercaptopropyl)-L-norvalinebenzylamide,

5

N-(2(R)-Amino-3-mercaptopropyl)isoleucyl-phenylalanyl-homoserine,

N-(2(R)-Amino-3-mercaptopropyl)isoleucyl-isoleucyl-homoserine,

10 N-(2(R)-Amino-3-mercaptopropyl)isoleucyl-phenylalanyl-homoserine
lactone,

N-(2(R)-Amino-3-mercaptopropyl)isoleucyl-isoleucyl-homoserine
lactone,

15

N-(2(R)-Amino-3-mercaptopropyl)isoleucyl-phenylalanyl-homocysteine
lactone,

20 N-[2(S)-(2(R)-Amino-3-mercaptopropyl)-3(S)-methylpentyl]-isoleucyl-
homoserine lactone,

N-[N'-(2(R)-Amino-3-mercaptopropyl)isoleucyl-phenylalanyl]-3(S)-
amino-tetrahydropyran-2-one,

25 N-[N'-(2(R)-Amino-3-mercaptopropyl)isoleucyl-isoleucyl]-3(S)-amino-
tetrahydropyran-2-one,

N-(2(R)-Amino-3-mercaptopropyl)isoleucyl-isoleucyl-homocysteine
lactone,

30

N-[2(S)-(2(R)-Amino-3-mercaptopropylamino)-3(S)-methyl
pentyl]isoleucyl-homoserine,

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N-[N'-(2(R)-Amino-3-mercaptopropyl)isoleucyl-phenylalanyl]-3(S)-amino-4-hydroxypentanoic acid,

5 N-[N'-(2(R)-Amino-3-mercaptopropyl)isoleucyl-isoleucyl]-3(S)-amino-4-hydroxypentanoic acid,

N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucyl-homoserine,

10 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucyl-homoserine lactone,

N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-phenylalanyl-homoserine,

15 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-phenylalanyl-homoserine lactone,

20 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3-methyl-butyl]-N-methyl-phenylalanyl-homoserine,

N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3-methyl-butyl]-N-methyl-phenylalanyl-homoserine lactone,

25 3(S)-{ N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucylamino }-3-methyltetra-hydropyran-2-one,

2(S)-{ N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucylamino }-2-methyl-5-hydroxypentanoic acid,

30 2(S)-{ N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucylamino }-5-methyl-5-hydroxyhexanoic acid,

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N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-norvalyl-homoserine,

5 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-norvalyl-homoserine lactone,

N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucyl-methionine,

10 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucyl-methionine methyl ester,

N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-phenylalanyl-methionine,

15 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-phenylalanyl-methionine methyl ester,

20 3(S)-{ N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-isoleucylamino }-6,6-dimethyl-tetrahydropyran-2-one,

N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-norvalyl-methionine,

25 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-norvalyl-methionine methyl ester,

N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-D-norvalyl-homoserine,

30 N-[2(S)-(2(R)-amino-3-mercaptopropylamino)-3(S)-methylpentyl]-N-methyl-D-norvalyl-homoserine lactone,

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2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-homoserine lactone,

5 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-2-methyl-3-phenylpropionyl-homoserine lactone,

10 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-4-pentenoyl-homoserine lactone,

15 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-4-pentenoyl-homoserine,

20 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxypentanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxypentanoyl-homoserine,

25 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-4-methylpentanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-4-methylpentanoyl-homoserine,

30 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-methylbutanoyl-homoserine lactone,

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- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-methylbutanoyl-homoserine,
- 5 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylbutanoyl-homoserine lactone,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylbutanoyl-homoserine,
- 10 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentylothio-2-methyl-3-phenylpropionyl-homoserine lactone,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentylothio-2-methyl-3-phenylpropionyl-homoserine,
- 15 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine lactone,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
20 pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-methionine methyl ester,
- 25 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-methionine,
- 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester,
- 30 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-phenylpropionyl-methionine sulfone,

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- 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-naphth-2-yl-propionyl-methionine sulfone methyl ester,
- 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
5 pentyloxy-3-naphth-2-yl-propionyl-methionine sulfone,
- 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone methyl ester,
- 10 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone,
- 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-methybutanoyl-methionine methyl ester,
- 15 2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-
pentyloxy-3-methybutanoyl-methionine,
- Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-
20 methyl]pentyloxy-3-phenylpropionyl-homoserine lactone,
- Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-
methyl]pentyloxy-3-phenylpropionyl-homoserine,
- 25 Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-
methyl]pentyloxy-3-methylbutanoyl-methionine methyl ester.
- 1-[2-(R)-Amino-3-mercaptopropyl]-2(S)-(1-butyl)-4-(2,3-dimethyl-
benzoyl)piperazine dihydrochloride
- 30 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(n-butyl)-4-(1-
naphthoyl)piperazine

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- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-benzyl-4-[1-(2,3-dimethyl)benzoyl]piperazine
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(2-methoxy)ethyl-4-[1-(2,3-dimethyl)benzoyl]piperazine
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(2-methylthio)ethyl-4-[1-(2,3-dimethyl)benzoyl]piperazine
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(n-butyl)-4-[7-(2,3-dihydrobenzofuroyl)]piperazine
- 1-(2(R)-Amino-3-mercaptopropyl)-4-(1-naphthoyl)-2(S)-pyridinylcarboxyl-4-piperazine dihydrochloride
- Methyl 4-(2(R)-amino-3-mercaptopropyl)-1-(1-naphthylmethyl)piperazine-2-carboxylate hydrochloride
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(2-methoxyethyl)-4-(1-naphthoyl)piperazine
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-n-butyl-4-(8-quinolinylcarbonyl)piperazine
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(2-(1-propoxy)ethyl)-4-(1-naphthoyl)piperazine
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(3-methoxy-1-propyl)-4-(1-naphthoyl)piperazine
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(2-(1-propoxy)ethyl)-4-(8-quinolinoyl)piperazine
- 1-[2(R)-Amino-3-mercaptopropyl]-2(S)-[(3-pyridyl)methoxyethyl]-4-(1-naphthoyl)piperazine

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- 1-[2(R)-Amino-3-mercaptopropyl]-4-naphthoyl-2(S)-(2-phenylsulfonyl-ethyl)piperazine dihydrochloride
- 5 *bis*-1,1'-[2(R)-Amino-3-(2(S)-(2-methoxyethyl)-4-naphthoyl-1-piperazinyl)]propyl disulfide tetrahydrochloride
- bis*-1,1'-[2(R)-Amino-3-(4-naphthoyl-2(S)-(2-phenylsulfonyl-ethyl)-1-piperazinyl)]propyl disulfide tetrahydrochloride
- 10 1-[2(R)-Amino-3-mercaptopropyl]-4-naphthoyl-2(S)-(2-cyclopropyloxyethyl)piperazine dihydrochloride
- 15 1-[2(R)-Amino-3-mercaptopropyl]-4-(1-naphthoyl)-2(S)-(4-acetamidobutyl)piperazine dihydrochloride
- 1-[2(R)-Amino-3-mercaptopropyl]-4-naphthoyl-2(S)-(2-cyclopropylmethylsulfonyl-ethyl)piperazine dihydrochloride
- 20 Pyroglutamyl-valyl-phenylalanyl-methionine
- Pyroglutamyl-valyl-phenylalanyl-methionine methyl ester;
- Pyroglutamyl-valyl-isoleucyl-methionine;
- 25 Pyroglutamyl-valyl-isoleucyl-methionine methyl ester;
- Nicotinoyl-isoleucyl-phenylalanyl-methionine;
- 30 Nicotinoyl-isoleucyl-phenylalanyl-methionine methyl ester;
- N-[2(S)-(L-Pyroglutamyl-amino)-3-methylbutyl]phenylalanyl-methionine;

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N-[2(S)-(L-Pyroglutamylamino)-3-methylbutyl]phenylalanyl-methionine methyl ester;

5 N-[5(S)-(L-Pyroglutamylamino)-6(S)-methyl-2(R)-butyl-3,4(E)-octenoyl]-methionine;

N-[5(S)-(L-Pyroglutamylamino)-6(S)-methyl-2(R)-butyl-3,4(E)-octenoyl]-methionine methyl ester;

10 N-[5(S)-((Imidazol-4-yl)acetyl amino)-6(S)-methyl-2(R)-butyl-3,4(E)-octenoyl]-methionine;

N-[5(S)-((Imidazol-4-yl)acetyl amino)-6(S)-methyl-2(R)-butyl-3,4(E)-octenoyl]-methionine methyl ester;

15 N-[5(S)-((Imidazol-4-yl)carbonylamino)-6(S)-methyl-2(R)-butyl-3,4(E)-octenoyl]-methionine;

20 N-[5(S)-((Imidazol-4-yl)carbonylamino)-6(S)-methyl-2(R)-butyl-3,4(E)-octenoyl]-methionine methyl ester;

N-[2(S)-(2(S)-(Imidazol-4-yl)acetyl amino)-3(S)-methylpentyl oxy)-3-phenylpropionyl]-methionine;

25 N-[2(S)-(2(S)-(Imidazol-4-yl)acetyl amino)-3(S)-methylpentyl oxy)-3-phenylpropionyl]-methionine methyl ester;

N-[2(S)-(2(S)-Pyroglutamyl amino-3(S)-methylpentyl oxy)-3-phenylpropionyl]-methionine;

30 N-[2(S)-(2(S)-Pyroglutamyl amino-3(S)-methylpentyl oxy)-3-phenylpropionyl]-methionine methyl ester;

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N-[2(S)-(2(S)-Imidazol-4-ylcarbonyl)amino)-3(S)-methylpentyl]-3-phenylpropionyl]-methionine;

5 N-[2(S)-(2(S)-Imidazol-4-ylcarbonyl)amino)-3(S)-methylpentyl]-3-phenylpropionyl]-methionine methyl ester;

N-[2(S)-(2(S)-((3-Picolinyl)amino)-3(S)-methylpentyl)-3-phenylpropionyl]-methionine;

10 N-[2(S)-(2(S)-((3-Picolinyl)amino)-3(S)-methylpentyl)-3-phenylpropionyl]-methionine methyl ester;

N-[2(S)-(2(S)-((Histidyl)amino)-3(S)-methylpentyl)-3-phenylpropionyl]-methionine;

15 N-[2(S)-(2(S)-((Histidyl)amino)-3(S)-methylpentyl)-3-phenylpropionyl]-methionine methyl ester;

20 N-Benzyl-N-[2(S)-((Imidazol-4-ylcarbonyl)amino)-3(S)-methylpentyl]-glycyl-methionine;

N-Benzyl-N-[2(S)-((Imidazol-4-ylcarbonyl)amino)-3(S)-methylpentyl]-glycyl-methionine methyl ester;

25 N-Benzyl-N-[2(S)-((Imidazol-4-ylacetyl)amino)-3(S)-methylpentyl]-glycyl-methionine;

N-Benzyl-N-[2(S)-((Imidazol-4-ylacetyl)amino)-3(S)-methylpentyl]-glycyl-methionine methyl ester;

30 N-Benzyl-N-[2(S)-((Pyroglutamyl)amino)-3(S)-methylpentyl]-glycyl-methionine;

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N-Benzyl-N-[2(S)-((Pyroglutamyl)amino)-3(S)-methylpentyl]-glycyl-methionine methyl ester;

5 N-(1-Naphthylmethyl)-N-[2(S)-((imidazol-4-ylcarbonyl)amino)-3(S)-methylpentyl]-glycyl-methionine;

N-(1-Naphthylmethyl)-N-[2(S)-((imidazol-4-ylcarbonyl)amino)-3(S)-methylpentyl]-glycyl-methionine methyl ester;

10 N-(1-Naphthylmethyl)-N-[2(S)-((imidazol-4-ylacetyl)amino)-3(S)-methylpentyl]-glycyl-methionine;

N-(1-Naphthylmethyl)-N-[2(S)-((imidazol-4-ylacetyl)amino)-3(S)-methylpentyl]-glycyl-methionine methyl ester;

15 N-(1-Naphthylmethyl)-N-[2(S)-((pyroglutamyl)amino-3(S)-methylpentyl)-glycyl-methionine; and

20 N-(1-Naphthylmethyl)-N-[2(S)-((pyroglutamyl)amino-3(S)-methylpentyl)-glycyl-methionine methyl ester;

N-[1-(Pyroglutamylamino)cyclopent-1-ylmethyl]-N-(1-naphthylmethyl)-glycyl-methionine methyl ester

25 N-[1-(Pyroglutamylamino)-cyclopent-1-ylmethyl]-N-(1-naphthylmethyl)-glycyl-methionine

N-(2(S)-L-Histidylamino-3(S)-methylpentyl)-N-(benzylmethyl)glycyl-methionine methyl ester

30 N-(2(S)-L-Histidylamino-3(S)-methylpentyl)-N-(benzylmethyl)glycyl-methionine

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- N-(2(S)-L-Histidylamino-3(S)-methylpentyl)-N-(1-naphthylmethyl)-glycyl-methionine methyl ester
- 5 N-(2(S)-L-Histidylamino-3(S)-methylpentyl)-N-(1-naphthylmethyl)-glycyl-methionine
- 2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-methylbutanoyl-methionine methyl ester
- 10 2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-methylbutanoyl-methionine
- 2(S)-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyloxy]-3-methylbutanoyl-methionine methyl ester
- 15 2(S)-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyloxy]-3-methylbutanoyl-methionine
- N-(Benzyl)-N-[2(S)-(2-oxopyrrolidin-5(R,S)-ylmethyl)amino-3(S)-methylpentyl]-glycyl-methionine methyl ester
- 20 N-(Benzyl)-N-[2(S)-(2-oxopyrrolidin-5(R,S)-ylmethyl)amino-3(S)-methylpentyl]-glycyl-methionine
- 25 N-(Benzyl)-N-{2(S)-[((D,L)-2-thiazolyl)alanyl]amino}-3(S)-methylpentyl}-glycyl-methionine methyl ester
- N-(Benzyl)-N-{2(S)-[((D,L)-2-thiazolyl)alanyl]amino}-3(S)-methylpentyl}-glycyl-methionine
- 30 N-(Benzyl)-N-[2(S)-(3-pyridylmethyl)amino-3(S)-methylpentyl]-glycyl-methionine methyl ester
- N-(Benzyl)-N-[2(S)-(3-pyridylmethyl)amino-3(S)-methylpentyl]-glycyl-methionine
- 35

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- 2(S)-[2(S)-(2-Oxopyrrolidin-5(S)-ylmethyl)amino-3(S)-methylpentyloxy]-3-phenylpropionyl-methionine methyl ester
- 5 2(S)-[2(S)-(2-Oxopyrrolidin-5(S)-ylmethyl)amino-3(S)-methylpentyloxy]-3-phenylpropionyl-methionine
- 2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-(1-naphthyl)propionyl-methionine sulfone methyl ester
- 10 2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-(1-naphthyl)propionyl-methionine sulfone
- 2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-(2-naphthyl)propionyl-methionine sulfone methyl ester
- 15 2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-(2-naphthyl)propionyl-methionine sulfone
- 2(S)-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyloxy]-3-(1-naphthyl)propionyl-methionine sulfone methyl ester
- 20 2(S)-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyloxy]-3-(1-naphthyl)propionyl-methionine sulfone
- 25 2(S)-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyloxy]-3-(2-naphthyl)propionyl-methionine sulfone methyl ester
- 2(S)-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyloxy]-3-(2-naphthyl)propionyl-methionine sulfone
- 30 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(3-quinolylmethyl)glycyl-methionine methyl ester

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N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(3-quinoly-
lmethyl)glycyl-methionine

5 N-(Benzyl)-N-[2(S)-(tetrazol-1-ylacetyl)amino-3(S)-methylpentyl]-
glycyl-methionine methyl ester

N-(Benzyl)-N-[2(S)-(tetrazol-1-ylacetyl)amino-3(S)-methylpentyl]-
glycyl-methionine

10 N-(Benzyl)-N-[2(S)-nicotinoylamino-3(S)-methylpentyl]-glycyl-
methionine methyl ester

N-(Benzyl)-N-[2(S)-nicotinoylamino-3(S)-methylpentyl]-glycyl-
methionine

15 N-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-
naphthylmethyl)-glycyl-methionine sulfoxide methyl ester

20 N-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-
naphthylmethyl)-glycyl-methionine sulfoxide

2(S)-{2(S)-[2(S,R)-(Imidazol-4-yl)-2-aminoacetyl]amino}-3(S)-
methylpentyloxy}-3-phenylpropionyl-methionine sulfone methyl ester

25 2(S)-{2(S)-[2(S,R)-(Imidazol-4-yl)-2-aminoacetyl]amino}-3(S)-
methylpentyloxy}-3-phenylpropionyl-methionine sulfone

2(S)-{2(S)-[2(R,S)-(Imidazol-4-yl)-2-aminoacetyl]amino}-3(S)-
methylpentyloxy}-3-phenylpropionyl-methionine sulfone methyl ester

30 2(S)-{2(S)-[2(R,S)-(Imidazol-4-yl)-2-aminoacetyl]amino}-3(S)-
methylpentyloxy}-3-phenylpropionyl-methionine sulfone

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N-{2(S)-[2(S,R)-(Imidazol-4-yl)-2-aminoacetyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)-glycyl-methionine methyl ester

5 N-{2(S)-[2(S,R)-(Imidazol-4-yl)-2-aminoacetyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)-glycyl-methionine

N-{2(S)-[2(R,S)-(Imidazol-4-yl)-2-aminoacetyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)-glycyl-methionine methyl ester

10 N-{2(S)-[2(R,S)-(Imidazol-4-yl)-2-aminoacetyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)-glycyl-methionine

15 N-{2(S)-[(Imidazol-4-yl)methyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)-glycyl-methionine methyl ester

N-{2(S)-[(Imidazol-4-yl)methyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)-glycyl-methionine

20 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-methionine t-butyl ester

25 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(4-quinolylmethyl)glycyl-methionine methyl ester

30 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(4-quinolylmethyl)glycyl-methionine

N-{2(S)-[3-(Imidazol-4-yl)propyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)glycyl-methionine methyl ester

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N-{2(S)-[3-(Imidazol-4-yl)propyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)glycyl-methionine

5 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-norleucine

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-norleucine methyl ester

10 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-glutamine

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-glutamine t-butyl ester

15 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-[5-(dimethylamino)naphthylsulfonyl]glycyl-methionine methyl ester

20 N-[2(S)-(3-pyridylmethyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-methionine

2(S)-{2(S)-[2-(Imidazol-4-yl)ethyl]amino-3(S)-methylpentyl}oxy-3-phenylpropionyl-methionine sulfone methyl ester

25 2(S)-{2(S)-[2-(Imidazol-4-yl)ethyl]amino-3(S)-methylpentyl}oxy-3-phenylpropionyl-methionine sulfone

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-serine methyl ester

30 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-(D,L)-serine

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- N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-(L,D)-serine
- 5 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-homoserine lactone
- N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-homoserine
- 10 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(cinnamyl)-glycyl-methionine methyl ester
- N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(cinnamyl)-glycyl-methionine
- 15 N-{2(S)-[2-(Imidazol-4-yl)ethyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)glycyl-methionine methyl ester
- N-{2(S)-[2-(Imidazol-4-yl)ethyl]amino-3(S)-methylpentyl}-N-(1-naphthylmethyl)glycyl-methionine
- 20 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-alanine methyl ester
- 25 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-alanine
- N-[2(S)-(D-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-methionine methyl ester
- 30 N-[2(S)-(D-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-methionine

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2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-phenyl-
propionyl-methionine sulfone methyl ester

5 2(S)-[2(S)-(L-Pyroglutamyl)amino-3(S)-methylpentyloxy]-3-phenyl-
propionyl-methionine sulfone

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(2,3-methyl-
enedioxybenzyl)glycyl-methionine methyl ester

10 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(2,3-
methylenedioxybenzyl)glycyl-methionine

15 N-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyl]-N-(2,3-
dihydrobenzofuran-7-ylmethyl)glycyl-methionine methyl ester

N-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyl]-N-(2,3-
dihydrobenzofuran-7-ylmethyl)glycyl-methionine

20 N-{2(S)-[3-(3-indolyl)propionyl]amino-3(S)-methylpentyl}-N-(1-
naphthylmethyl)glycyl-methionine methyl ester

N-{2(S)-[3-(3-indolyl)propionyl]amino-3(S)-methylpentyl}-N-(1-
naphthylmethyl)glycyl-methionine

25 N-{2(S)-[3-(1-indolyl)propionyl]amino-3(S)-methylpentyl}-N-(1-
naphthylmethyl)glycyl-methionine methyl ester

30 N-{2(S)-[3-(1-indolyl)propionyl]amino-3(S)-methylpentyl}-N-(1-
naphthylmethyl)glycyl-methionine

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-
naphthylmethyl)glycyl-histidine methyl ester

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- N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-histidine
- 5 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(cyclopropylmethyl)glycyl-methionine methyl ester
- N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(cyclopropylmethyl)glycyl-methionine
- 10 N-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyl]-N-(cyclopropylmethyl)glycyl-methionine methyl ester
- N-[2(S)-(Imidazol-4-ylacetyl)amino-3(S)-methylpentyl]-N-(cyclopropylmethyl)glycyl-methionine
- 15 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(2,3-dihydrobenzofuran-7-ylmethyl)glycyl-methionine methyl ester
- N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(2,3-dihydrobenzofuran-7-ylmethyl)glycyl-methionine
- 20 2(S)-[2(S)-N-(L-Pyroglutamyl)-N-methylamino-3(S)-methylpentyloxy]-3-phenylpropionyl-methionine methyl ester
- 25 2(S)-[2(S)-N-(L-Pyroglutamyl)-N-methylamino-3(S)-methylpentyloxy]-3-phenylpropionyl-methionine
- N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-O-methylserine methyl ester
- 30 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-O-methylserine
- N-(1-Naphthylmethyl)-N-[2(S)-(N'-(L-pyroglutamyl)-N'-methylamino)-3(S)-methylpentyl]-glycyl-methionine methyl ester
- 35

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N-(1-Naphthylmethyl)-N-[2(S)-(N'-(L-pyroglutamyl)-N'-methylamino)-3(S)-methylpentyl]-glycyl-methionine

5 N-[1-(Pyroglutamylamino)cyclopent-1-ylmethyl]-N-(1-naphthylmethyl)-glycyl-methionine methyl ester

N-[1-(Pyroglutamylamino)-cyclopent-1-ylmethyl]-N-(1-naphthylmethyl)-glycyl-methionine

10

N-[2(S)-(Pyridin-2-on-6-ylcarbonyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester

15 N-[2(S)-(Pyridin-2-on-6-ylcarbonyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-methionine

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(3-chlorobenzyl)glycyl-methionine methyl ester

20 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(3-chlorobenzyl)glycyl-methionine

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-O-methylhomoserine methyl ester

25

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-O-methylhomoserine

30 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(2,3-dimethylbenzyl)glycyl-methionine methyl ester

N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(2,3-dimethylbenzyl)glycyl-methionine

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N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-(2-thienyl)alanine methyl ester

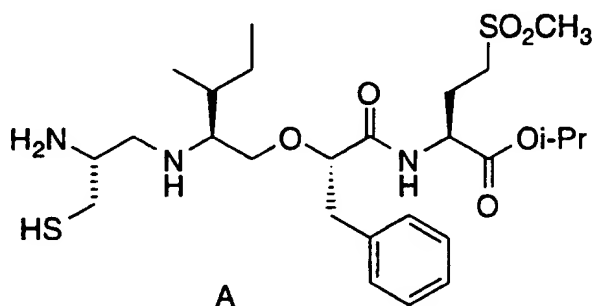
5 N-[2(S)-(L-pyroglutamyl)amino-3(S)-methylpentyl]-N-(1-naphthyl-methyl)glycyl-(2-thienyl)alanine

N-[2(S)-(pyrrolidin-2-on-1-yl)-3-methylbutanoyl]-isoleucyl-methionine;
or

10 N-[2(S)-(piperidin-2-on-1-yl)-3-methylbutanoyl]-isoleucyl-methionine;

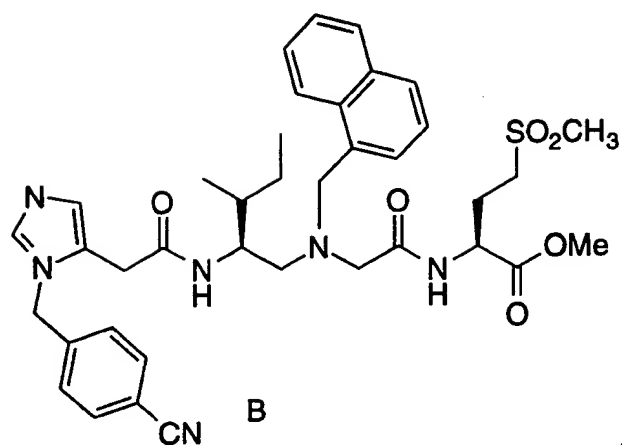
or a pharmaceutically acceptable salt or optical isomer thereof.

15 7. The method according to Claim 5 wherein the protein substrate competitive inhibitor is selected from:
Compound A:

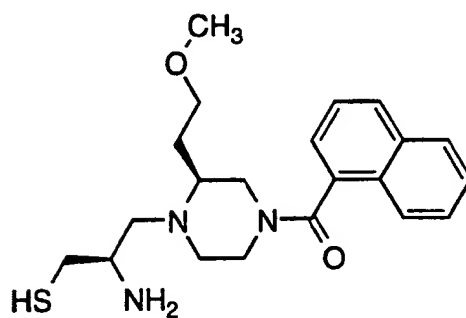


20 Compound B:

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and Compound E:



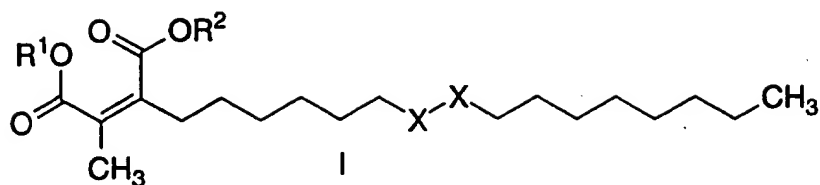
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or a pharmaceutically acceptable salt or optical isomer thereof.

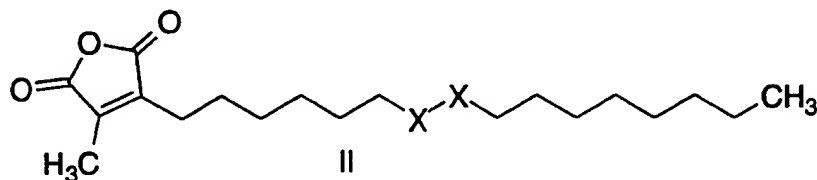
8. The method according to Claim 1 wherein the
10 farnesyl pyrophosphate-competitive inhibitor is selected from:

bb)

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or



wherein:

5 X - X is: CH = CH (cis);
CH = CH (trans); or
CH₂CH₂;

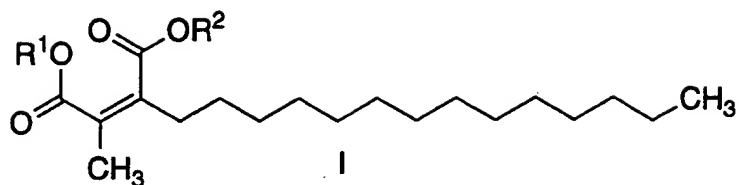
R¹ and R² are each independently selected from:

- 10 a) H;
b) C₁₋₅ alkyl;
c) C₁₋₅ alkyl substituted with a member of the group
consisting of:
i) phenyl;
ii) phenyl substituted with methyl, methoxy, halogen
15 (Cl, Br, F, I) or hydroxy;

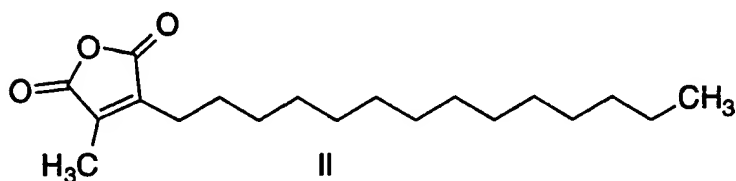
or a pharmaceutically acceptable salt of a compound of formula (I) in
which at least one of R¹ and R² is hydrogen;

20 cc)

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or



wherein:

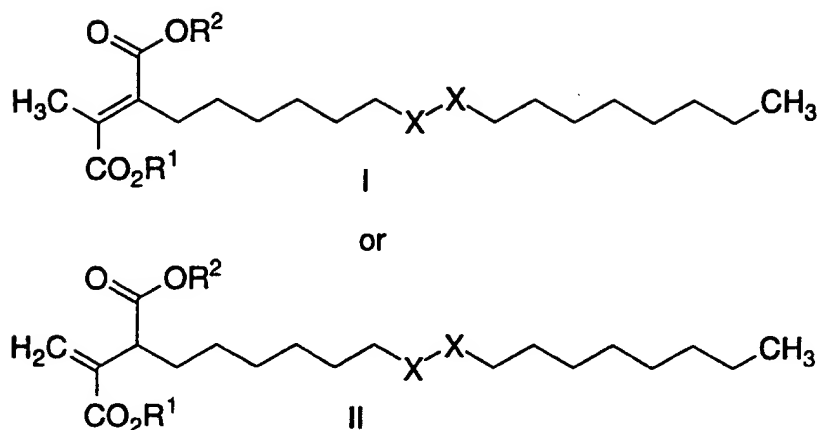
 R^1 and R^2 are each independently selected from:

- a) H;
- b) C₁₋₅ alkyl;
- c) C₁₋₅ alkyl substituted with a member of the group consisting of:
 - i) phenyl;
 - ii) phenyl substituted with methyl, methoxy, halogen (Cl, Br, F, I) or hydroxy;

or a pharmaceutically acceptable salt of a compound of formula (I) in which at least one of R^1 and R^2 is hydrogen;

dd)

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wherein:

X - X is: CH = CH (cis);
CH = CH (trans); or
CH₂CH₂;

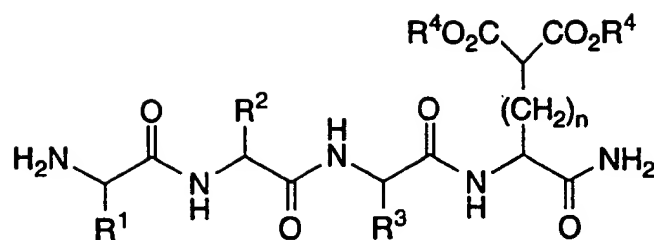
R¹ and R² are each independently selected from:

- a) H;
- b) C₁-5 alkyl;
- c) C₁-5 alkyl substituted with a member of the group consisting of:
 - i) phenyl;
 - ii) phenyl substituted with methyl, methoxy, halogen (Cl, Br, F, I) or hydroxy;

or a pharmaceutically acceptable salt of a compound of formula (I) in which at least one of R¹ and R² is hydrogen;

ee)

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I

or the pharmaceutically acceptable salts, hydrates, esters or amides thereof, wherein:

5 n is: 0 to 4,

R^1 and R^3 independently are C₀₋₄ alkyl, substituted with substituents selected from the group consisting of:

10 a) aryl, which is defined as phenyl or naphthyl, unsubstituted or substituted with one, two, three or four substituents selected from the group consisting of:

- 15 i) F,
 ii) Cl,
 iii) Br,
 iv) nitro,
 v) cyano,
 vi) C₁₋₈ alkoxy,
 vii) C₁₋₈ alkylthio,
 viii) C₁₋₈ alkylsulfonyl,
 20 ix) sulfamoyl, or
 x) C₁₋₈ alkyl; or

b) heteroaryl, which is defined as indolyl, imidazolyl or pyridyl, unsubstituted or substituted with one, two, three or four substituents selected from the group consisting of:

25

- i) F,
 ii) Cl,
 iii) Br,

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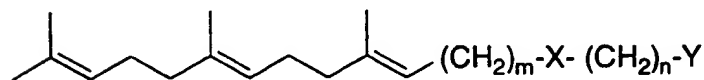
- 5
 iv) nitro,
 v) cyano,
 vi) C₁₋₈ alkoxy,
 vii) C₁₋₈ alkylthio,
 viii) C₁₋₈ alkylsulfonyl,
 ix) sulfamoyl, or
 x) C₁₋₈ alkyl;

10 R² is: C₀₋₆ alkyl, which is unsubstituted or substituted with a substituent selected from the group consisting of:

- 15
 a) unsubstituted or substituted aryl, as defined in R¹(a),
 b) unsubstituted or substituted heteroaryl, as defined in R¹(b),
 c) C₃₋₈ cycloalkyl,
 d) C₁₋₈ alkylthio,
 e) C₁₋₈ alkylsulfonyl,
 f) C₁₋₈ alkoxy, or
 g) aryl C₁₋₈ alkyl sulfonyl; and

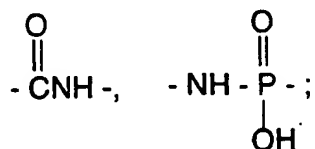
20 R⁴ is: H;

ff)



wherein:

25 X is CH₂, CH(OH), C=O, CHCOR, CH(NH₂), CH(NHCOR), O, S(O)_p, NH, NHCO,



p is 0, 1 or 2;

Y is PO₃RR¹ or CO₂R;

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R is H, lower alkyl, or $\text{CH}_2\text{CH}_2\text{N}^+\text{Me}_3\text{A}^-$;

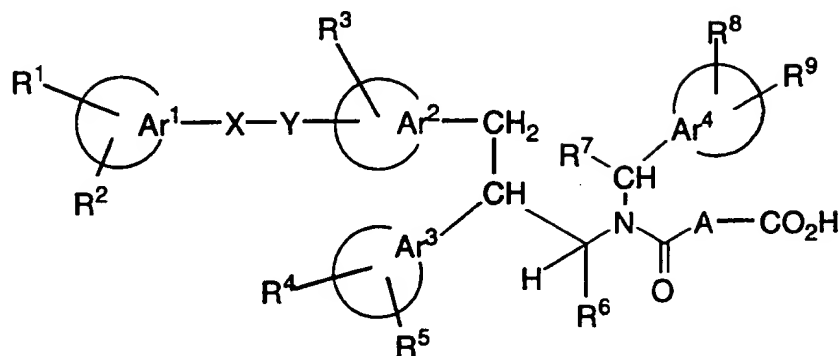
R^1 is H, lower alkyl, or $\text{CH}_2\text{CH}_2\text{N}^+\text{Me}_3\text{A}^-$;

A is a pharmaceutically acceptable anion;

m is 0, 1, 2, or 3; and

5 n is 0, 1, 2, or 3;

gg)



10 wherein each of



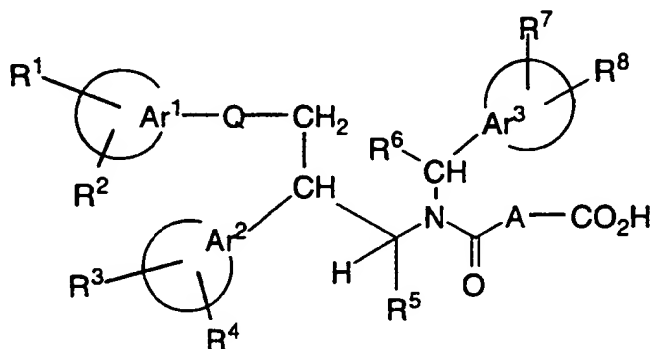
15 which are the same or different, is an aryl group or a heteroaromatic ring group; A is a C2-8 saturated or unsaturated aliphatic hydrocarbon group which may have substituent(s) selected from the group consisting of a lower alkyl group, a hydroxyl group, a lower hydroxyalkyl group, a lower alkoxy group, a carboxyl group, a lower carboxyalkyl group, an aryl group and an aralkyl group; each of X and Y which are the same or different, is an oxygen atom, a sulfur atom, a
 20 carbonyl group or a group of the formula $-\text{CHR}^a-$ (wherein R^a is a hydrogen atom or a lower alkyl group) or $-\text{NR}^b$ (wherein R^b is a hydrogen atom or a lower alkyl group), or X and Y together represent a vinylene group or an ethynylene group; each of R^1 , R^2 , R^3 , R^8 and R^9 which are the same or different, is a hydrogen atom, a halogen atom, a

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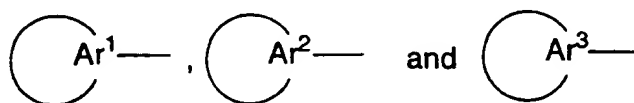
hydroxyl group, a lower alkyl group or a lower alkoxy group; each of R^4 and R^5 which are the same or different, is a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, a carboxyl group, a lower alkoxycarbonyl group, a carbamoyl group, a lower alkylcarbamoyl group, a lower alkyl group, a lower hydroxyalkyl group, a lower fluoroalkyl group or a lower alkoxy group; R^6 is a lower alkyl group; and R^7 is a hydrogen atom or a lower alkyl group, provided that when one of X and Y is an oxygen atom, a sulfur atom or a group of the formula $-NR^b$ - (wherein R^b is as defined above), the other is a carbonyl group or a group of the formula $-CHR^a$ - (wherein R^a is as defined above);

or

15 hh)



wherein each of



20 which are the same or different, is an aryl group or a heteroaromatic ring group; A is a C2-8 saturated or unsaturated aliphatic hydrocarbon group which may have substituent(s) selected from the group consisting of a lower alkyl group, a hydroxyl group, a lower hydroxyalkyl group,

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a lower alkoxy group, a carboxyl group, a lower carboxyalkyl group, an aryl group and an aralkyl group; Q is a group of the formula $-(C_1-12)_m-$ (wherein m is an integer of from 1 to 6) or $-(CH_2)_n-W-(CH_2)_p-$ (wherein W is an oxygen atom, a sulfur atom, a vinylene group or an ethynylene group; and each of n and p which are the same or different is an integer of from 0 to 3); R^1 is a hydrogen atom, a halogen atom, a hydroxyl group, a lower alkyl group, a lower alkoxy group, or an aryl or heteroaromatic ring group which may have substituent(s) selected from the group consisting of a halogen atom, a lower alkyl group and a lower alkoxy group; each of R^2 , R^7 and R^8 which are the same or different, is a hydrogen atom, a halogen atom, a hydroxyl group, a lower alkyl group or a lower alkoxy group; each of R^3 and R^4 which are the same or different, is a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, a carboxyl group, a lower alkoxy carbonyl group, a carbamoyl group, a lower alkyl carbamoyl group, a lower alkyl group, a lower hydroxyalkyl group, a lower fluoroalkyl group or a lower alkoxy group; R^5 is a lower alkyl group; and R^6 is a hydrogen atom or a lower alkyl group;

or a pharmaceutically acceptable salt thereof.

9. The method according to Claim 8 wherein the farnesyl pyrophosphate-competitive inhibitor is selected from:
- 3-Hydroxy-7,11,15-trimethylhexadeca-6,10,14-trienoic acid,
- [2- Oxo-6,10,14-trimethylpentadeca-5,9,13-trienyl]phosphonic acid
- [2- Hydroxy-6,10,14-trimethylpentadeca-5,9,13-trienyl]phosphonic acid
- [1- Acetyl-4,8,12-trimethylpentadeca-3,7,11-trienyl]phosphonic acid

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- [2-[(E,E)-3,7,11-Trimethyl-2,6,10-dodecatrienylamino]-2-oxo-ethyl]phosphonic acid
- 5 [(E,E)-4,8,12-Trimethyl-3,7,11-tridecatrienyl]thiomethyl-phosphonic acid
- 3-[(E,E)-3,7,11-Trimethyl-2,6,10-dodecatrienylamino]-3-oxo-propionic acid
- 10 [2-[(E,E)-3,7,11-Trimethyl-2,6,10-dodecatrienylamino]-2-oxo-ethyl]phosphonic acid monomethyl ester
- [2-[(E,E)-3,7,11-Trimethyl-2,6,10-dodecatrienylamino]-1-oxo-methyl]phosphonic acid
- 15 [1-Hydroxy-(E,E)-3,7,11-trimethyl-2,6,10-dodecatrienyl]-phosphonic acid
- [1-Hydroxy-(E,E)-5,9,13-trimethyl-4,8,12-tetradecatrienyl]-phosphonic acid
- 20 [1-Hydroxy-(E,E)-4,8,12-trimethyl-3,7,11-tridecatrienyl]-phosphonic acid
- [2-Acetamido-(E,E)-4,8,12-trimethyl-3,7,11-tridecatrienyl]-phosphonic acid,
- 25 [2-Hydroxy-(E,E)-4,8,12-trimethyl-3,7,11-tridecatrienyl]-phosphonic acid
- 30 N-{(1R,2R,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

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N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(1-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

5 N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)pentyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-4-(2-naphthoxy)butyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

10 N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-4-(2-naphthyl)butyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-6-(2-naphthyl)hexyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

15 N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-5-phenyl-4-pentynyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

20 N-{(1RS,2RS,4E)-2-(4-methoxyphenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

N-{(1RS,2RS,4E)-1-methyl-2-(4-methylphenyl)-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

25 N-{(1RS,2RS,4E)-1-methyl-5-(2-naphthyl)-2-(4-nitrophenyl)-4-pentenyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

N-{(1RS,2RS,4E)-2-(4-fluorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

30 N-{(1RS,2RS,4E)-1-methyl-5-(2-naphthyl)-2-(4-trifluoromethylphenyl)-4-pentenyl}-N-(2-naphthylmethyl)-carbamoylmethylsuccinic acid

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- N-{(IRS,2RS,4E)-1-methyl-5-(2-naphthyl)-2-phenyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylethylsuccinic acid
- 5 N-{(IRS,2RS,4E)-1-methyl-2-(6-methyl-3-pyridyl)-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylethylsuccinic acid
- N-{(IRS,2RS,6E)-2-(4-chlorophenyl)-1-methyl-7-phenyl-6-heptenyl}-N-(2-naphthylmethyl)carbamoylethylsuccinic acid
- 10 N-{(IRS,2RS,6E)-2-(4-chlorophenyl)-1-methyl-7-(2-naphthyl)-6-heptenyl}-N-(2-naphthylmethyl)carbamoylethylsuccinic acid
- N-{(IRS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(3-quinolylmethyl)carbamoylethylsuccinic acid
- 15 N-{(IRS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(3,4-difluorobenzyl)carbamoylethylsuccinic acid
- N-(2-benzoxazolylmethyl)-N-{(IRS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}carbamoylethylsuccinic acid
- 20 N-(2-benzo[b]thienylmethyl)-N-{(IRS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}carbamoylethylsuccinic acid
- 25 N-{(IRS,2RS,4E)-1-methyl-2-(3,4-methylenedioxyphenyl)-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylethylsuccinic acid
- (2R*)-2-[N-{(1S*,2S*,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylethyl]succinic acid
- 30 (2R*)-2-[N-{(1R*,2R*,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylethyl]succinic acid

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- (2S*)-2-[N-{(1R*,2R*,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- 5 (2S*)-2-[N-{(1S*,2S*,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- 5-[N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]pentanoic acid
- 10 (2R*)-2-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- 15 (2R*)-2-[N-{(1RS,2RS,4Z)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- 20 (2R*)-2-[N-(2-benzo[b]furanylmethyl)-N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}carbamoylmethyl]succinate
- 25 (2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}carbamoylmethyl]succinic acid
- 30 (2R*)-2-[N-[(1RS,2RS,4E)-5-(2-benzoxazolyl)-2-{3,4-bis(methoxycarbonyl)phenyl}-1-methyl-4-pentenyl]-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- (2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methyl-4-pentenyl}carbamoylmethyl]succinic acid

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(2R*)-2-[N-(2-benzo[b]furanylmethyl)-N-{(1R,2R,4E)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methyl-4-pentenyl}carbamoylmethyl]succinic acid

5 (2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-{(1R,2R,4E)-5-(2-benzoxazolyl)-2-(4-cyanophenyl)-1-methyl-4-pentenyl}carbamoylmethyl]succinic acid

10 (2R*)-2-[N-(5-benzo[b]thienylmethyl)-N-{(1R,2R,4E)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methyl-4-pentenyl}carbamoylmethyl]succinic acid

15 N-{(1R,2R,4E)-5-(3-chloro-4-methylphenyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

N-{(1R,2R,4Z)-5-(3-chloro-4-methylphenyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

20 N-{(1R,2R,4E)-5-(2-benzo[b]furanyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

N-{(1R,2R,4Z)-5-(2-benzo[b]furanyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

25 N-{(1R,2R,4E)-5-(2-benzoxazolyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

N-{(1R,2R,4Z)-5-(2-benzoxazolyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

30 N-{(1R,2R,4E)-5-(2-benzimidazolyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

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N-{(1RS,2RS,4E)-2-(4-chlorophenyl)-1-methyl-5-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

- 5 N-{(1RS,2RS,4E)-5-(2-benzothiazolyl)-2-(4-chlorophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-2-(4-cyanophenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

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4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-1,2,3-butanetricarboxylic acid

- 15 3-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-1,2,2-propanetricarboxylic acid

- 20 (2S,3R)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]-3-carboxy-2-hydroxybutanoic acid

- 25 4-[N-((1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl)-N-(2-naphthylmethyl)carbamoyl]-3-carboxy-4-methoxybutanoic acid

- 5-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-4-carboxy-3-carboxymethylpentanoic acid

30

1-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-1,2,3-propanetricarboxylic acid

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- (3R*)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-methoxybutanoic acid
- 5 (3S*)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-methoxybutanoic acid
- 10 N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-2-(4-carboxyphenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 15 N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-[4-(N-methylcarbamoyl)phenyl]-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- (2R*)-2-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-2-(4-hydroxy-3-methoxyphenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 20 N-{(1RS,2RS,4E)-2-(4-hydroxymethylphenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 25 N-{(1RS,2RS,4E)-2-(4-aminophenyl)-1-methyl-5-(2-naphthyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- disodium (3RS,4RS)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxy-4-hydroxybutanoate
- 30 N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)-5-oxotetrahydrofuran-2-carboxamide

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sodium 4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)]carbamoyl-4-hydroxybutanoate

5 4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-2-oxotetrahydrofuran-3-yl-acetic acid

10 (2R*)-2-[N-{(1R*,2R*,4E)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

15 (2R*)-2-[N-{(1S*,2S*,4E)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

20 (2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-{(1S*,2S*,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}carbamoylmethyl]succinic acid

(2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-{(1R*,2R*,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}carbamoylmethyl]succinic acid

25 (2R*)-2-[N-{(1RS,2RS)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)pentyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

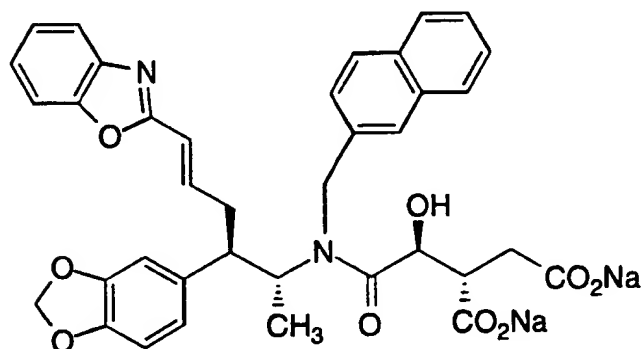
30 (2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-{(1RS,2RS)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-pentyl}carbamoylmethyl]succinic acid

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(2R*)-2-[N-{(1R*,2R*)-5-(2-benzoxazolyl)-2-(4-methoxycarbonylphenyl)-1-methylpentyl}-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

- 5 disodium (3S,4S)-4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxy-4-hydroxybutanoate (Compound D)

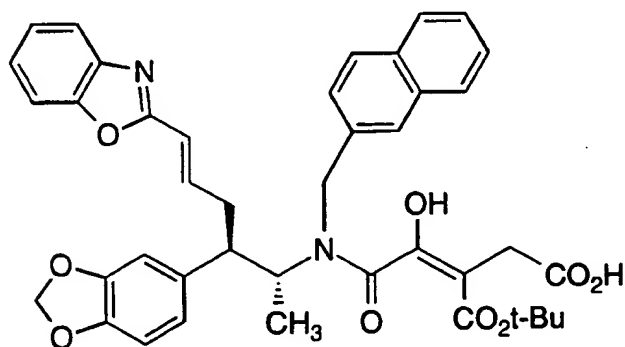
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- sodium (3S,4S)-4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-ethoxycarbonyl-4-hydroxybutanoate
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4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxy-3-butenic acid

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- 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-l-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
5 4-hydroxy-3-methoxycarbonyl-3-butenic acid
- 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-l-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
10 4-hydroxy-3-isopropoxycarbonyl-3-butenic acid
- 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-l-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
15 3-cyclohexyloxycarbonyl-4-hydroxy-3-butenic acid
- 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-l-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
20 4-hydroxy-3-(2-methoxyethoxy)carbonyl-3-butenic acid
- 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-l-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
25 3-cyclopentyloxycarbonyl-4-hydroxy-3-butenic acid
- 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-l-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
30 4-hydroxy-3-(3-tetrahydrofuranyloxycarbonyl)-3-butenic acid
- 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-l-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-
4-hydroxy-3-(2-hydroxy-1-hydroxymethylethoxycarbonyl)-3-butenic
acid

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- 3-allyloxycarbonyl-4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-4-hydroxy-3-butenic acid
- 5 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-2-(3,4-methylenedioxyphenyl)-1-methyl-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxymethylcarbonyl-4-hydroxy-3-butenic acid
- 10 5-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-4-ethoxycarbonyl-5-hydroxy-4-pentenoic acid
- 15 5-N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-4-tert-butoxycarbonyl-5-hydroxy-4-pentenoic acid
- 20 4-N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-4-hydroxy-3-hydroxymethyl-3-butenic acid
- 25 4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxy-3-butenic acid
- (2S*,3R*)-4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-1,2,3-butanetricarboxylic acid
- 30 (2R*,3S*)-4-[N-{(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-1,2,3-butanetricarboxylic acid

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N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

5 N-[(1RS,2RS)-3-{5-(3,4-dimethoxyphenylcarbamoyl)-2-furyl}-1-methyl-2-(4-nitrophenyl)propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

10 N-[(1RS,2RS)-3-{5-(2-hydroxyphenylcarbamoyl)-2-furyl}-1-methyl-2-(4-nitrophenyl)propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

N-[(1RS,2RS)-1-methyl-3-{5-(N-methylphenylcarbamoyl)-2-furyl}-2-(4-nitrophenyl)propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

15 N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(3-pyridylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

20 N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(4-pyridylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

25 N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(5-pyrimidinylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(2-thiazolylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

30 N-[(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

N-{(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-3-(3-phenylcarbamoylphenyl)propyl}-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid

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- N-[(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-3-{3-(phenylcarbamoyl)-5-isoxazolyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 5 N-[(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-3-{4-(phenylcarbamoyl)-2-pyridyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- (2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-[(1RS,2RS)-1-methyl-2-(3,4-methylenedioxyphenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]carbamoylmethyl]succinic acid
- 10 (2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-[(1RS,2RS)-1-methyl-2-(3,4-methylenedioxyphenyl)-3-{5-(3-pyridylcarbamoyl)-2-furyl}propyl]carbamoylmethyl]succinic acid
- 15 monopivaloyloxymethyl (2R*)-2-[N-(2-benzo[b]thienylmethyl)-N-[(1RS,2RS)-1-methyl-2-(3,4-methylenedioxyphenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]carbamoylmethyl]succinate
- 20 (2R*)-2-[N-{(1RS,2RS)-2-(4-methoxycarbonylphenyl)-1-methyl-3-(3-phenoxyethylphenyl)propyl}-N-2-naphthylmethyl]carbamoylmethyl]succinic acid
- (2R*)-2-[N-[(1RS,2RS)-2-(4-methoxycarbonylphenyl)-1-methyl-3-{3-(phenoxyethyl)-5-(1,2,4-oxadiazolyl)}propyl]-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- 25 (2R*)-2-[N-[(1RS,2RS)-2-(4-methoxycarbonylphenyl)-1-methyl-3-{(E)-3-styrylphenyl}propyl]-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid
- 30 (2R*)-2-[N-[(1RS,2RS)-2-(4-methoxycarbonylphenyl)-1-methyl-3-{3-(2-phenylethyl)phenyl}propyl]-N-(2-naphthylmethyl)carbamoylmethyl]succinic acid

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- N-[(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-3-(4-phenylethynylphenyl)-propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 5 N-[(1RS,2RS)-2-(4-chlorophenyl)-1-methyl-3-{(E)-3-styrylphenyl}propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 10 N-[(1RS,2RS)-2-(4-methoxycarbonylphenyl)-1-methyl-3-(5-phenoxyethyl-2-furyl)propyl]-N-(2-naphthylmethyl)carbamoylmethylsuccinic acid
- 15 4-[N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]-1,2,3-butanetricarboxylic acid
- 20 disodium (3RS,4RS)-3-carboxylato-4-hydroxy-4-[N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]butanoate
- disodium (3SR,4SR)-3-carboxylato-4-hydroxy-4-[N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]butanoate
- 25 3-tert-butoxycarbonyl-4-hydroxy-4-[N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]-3-butenic acid
- 30 3-tert-butoxycarbonyl-4-hydroxy-4-[N-[(1RS,2RS)-1-methyl-2-(3,4-methylenedioxyphenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]-3-butenic acid
- 3-tert-butoxycarbonyl-4-hydroxy-4-[N-[(1RS,2RS)-1-methyl-2-(4-nitrophenyl)-3-(3-phenoxyethylphenyl)propyl]-N-(2-

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naphthylmethyl)carbamoyl]-3-butenic acid

4-hydroxy-3-methoxycarbonyl-4-[N-[(1R,2R)-1-methyl-2-(3,4-methylenedioxyphenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]-3-butenic acid

3-allyloxycarbonyl-4-hydroxy-4-[N-[(1R,2R)-1-methyl-2-(3,4-methylenedioxyphenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]-3-butenic acid

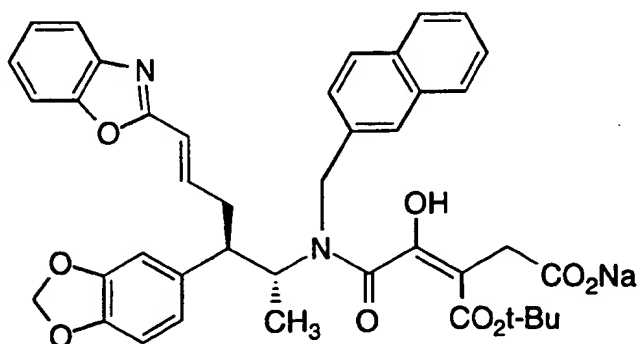
5-hydroxy-4-isopropylcarbonyl-5-[N-[(1R,2R)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]-N-(2-naphthylmethyl)carbamoyl]-4-pentenoic acid or

3-tert-butoxycarbonyl-4-{N-(2,3-dichlorobenzyl)-N-[(1R,2R)-1-methyl-2-(4-nitrophenyl)-3-{5-(phenylcarbamoyl)-2-furyl}propyl]carbamoyl}-4-hydroxy-3-butenic acid

or a pharmaceutically acceptable salt or optical isomer thereof.

10. The method according to Claim 8 wherein the farnesyl pyrophosphate-competitive inhibitor is selected from:

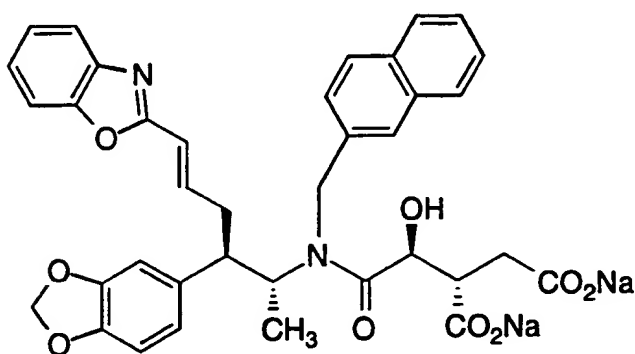
sodium 4-[N-[(1R,2R,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl]-N-(2-naphthylmethyl)carbamoyl]-3-tert-butoxycarbonyl-4-hydroxy-3-butenate (Compound C)



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or

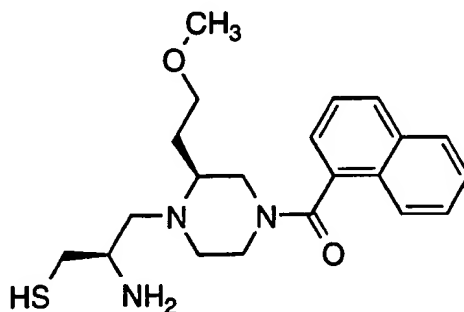
- 5 disodium (3RS,4RS)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-l-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxyl-4-hydroxybutanoate (Compound D)



10

or a pharmaceutically acceptable salt or optical isomer thereof.

11. The method according to Claim 1 wherein the protein substrate-competitive inhibitor is:
- 15 Compound E:

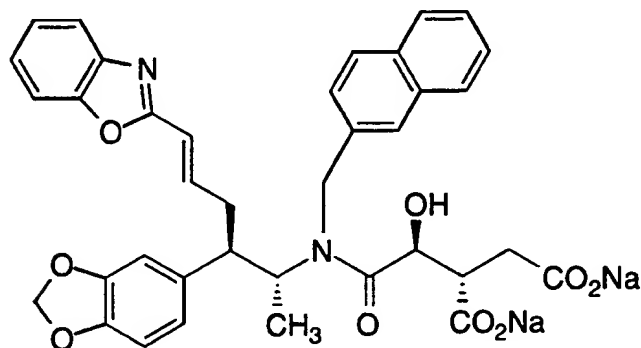


or a pharmaceutically acceptable salt or optical isomer thereof
and the farnesyl pyrophosphate-competitive inhibitor is:

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disodium (3RS,4RS)-4-[N-{(1RS,2RS,4E)-5-(2-benzoxazolyl)-1-methyl-2-(3,4-methylenedioxyphenyl)-4-pentenyl}-N-(2-naphthylmethyl)carbamoyl]-3-carboxyl-4-hydroxybutanoate (Compound D)

5



12. A pharmaceutical composition for achieving an additive or synergistic therapeutic effect in a mammal in need thereof which comprises amounts of at least two therapeutic agents selected from a group consisting of:

- 15 a) a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to the protein substrate of the enzyme and
- b) a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to farnesyl pyrophosphate;

20 wherein the amount of a) alone and the amount of b) alone is insufficient to achieve said therapeutic effect.

13. The pharmaceutical composition according to Claim 12 comprising an amount of a protein substrate-competitive inhibitor and an amount of a farnesyl pyrophosphate-competitive inhibitor.

14. A pharmaceutical composition for achieving a synergistic therapeutic effect in a mammal in need thereof which

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comprises amounts of at least two therapeutic agents selected from a group consisting of:

- 5 a) a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to the protein substrate of the enzyme and
- b) a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to farnesyl pyrophosphate;

10

wherein the amount of a) alone and the amount of b) alone is insufficient to achieve said therapeutic effect; and wherein said therapeutic effect of the pharmaceutical composition is greater than the sum of the therapeutic effects of the amounts of the

15 amounts of the individual therapeutic agents administered.

15. The pharmaceutical composition according to Claim 14 comprising an amount of a protein substrate-competitive inhibitor and an amount of a farnesyl pyrophosphate-competitive inhibitor.

20

16. A method of preparing a pharmaceutical composition for achieving an additive or synergistic therapeutic effect in a mammal in need thereof which comprises mixing amounts of at least two therapeutic agents selected from a group consisting of:

25

- a) a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to the protein substrate of the enzyme and
- 30 b) a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to farnesyl pyrophosphate;

wherein the amount of a) alone and the amount of b) alone is insufficient to achieve said therapeutic effect.

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17. The method of preparing a pharmaceutical composition according to Claim 16 comprising mixing an amount of a protein substrate-competitive inhibitor and an amount of a farnesyl pyrophosphate-competitive inhibitor.

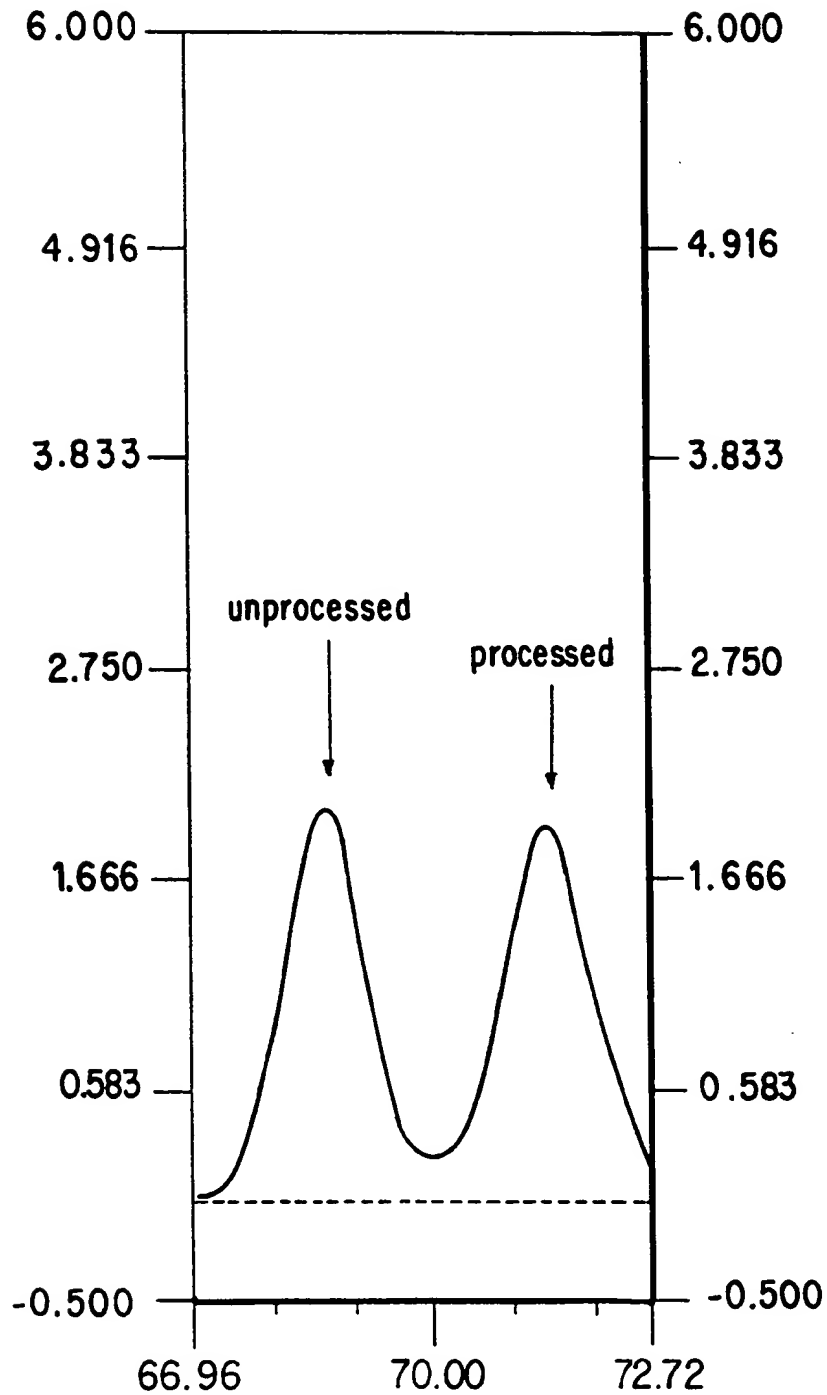
18. A method of preparing a pharmaceutical composition for achieving a synergistic therapeutic effect in a mammal in need thereof which comprises mixing amounts of at least two therapeutic agents selected from a group consisting of:

- a) a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to the protein substrate of the enzyme and
- b) a farnesyl protein transferase inhibitor which is an effective inhibitor of the enzyme because it is competitive with respect to farnesyl pyrophosphate;

wherein the amount of a) alone and the amount of b) alone is insufficient to achieve said therapeutic effect; and wherein said therapeutic effect of the pharmaceutical composition is greater than the sum of the therapeutic effects of the amounts of the amounts of the individual therapeutic agents administered.

19. The method of preparing a pharmaceutical composition according to Claim 18 comprising mixing an amount of a protein substrate-competitive inhibitor and an amount of a farnesyl pyrophosphate-competitive inhibitor.

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Compound D

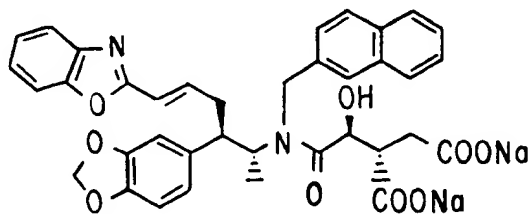
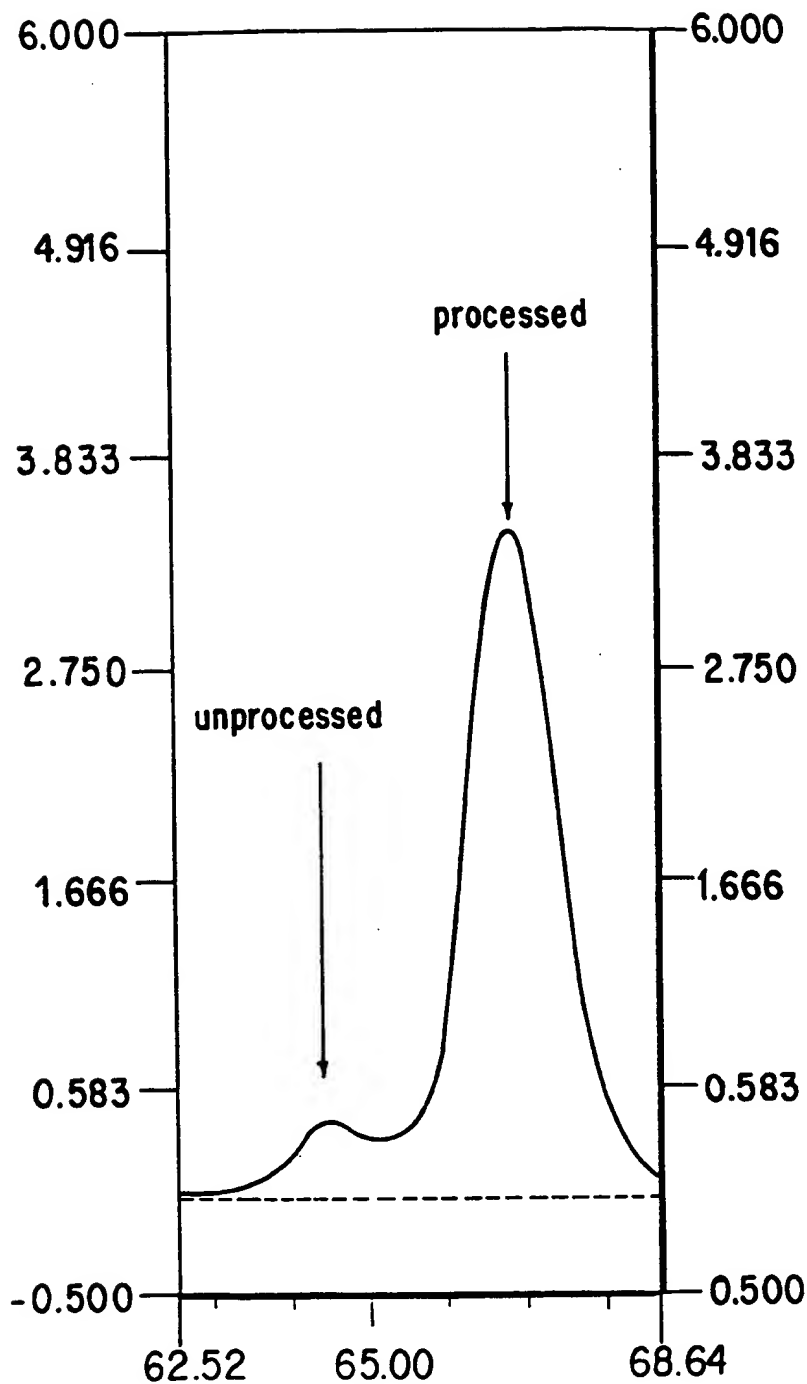


FIG. 1A



Compound E

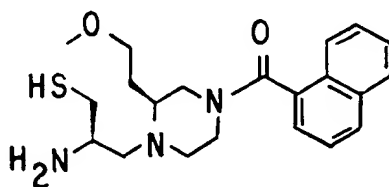


FIG. 1B

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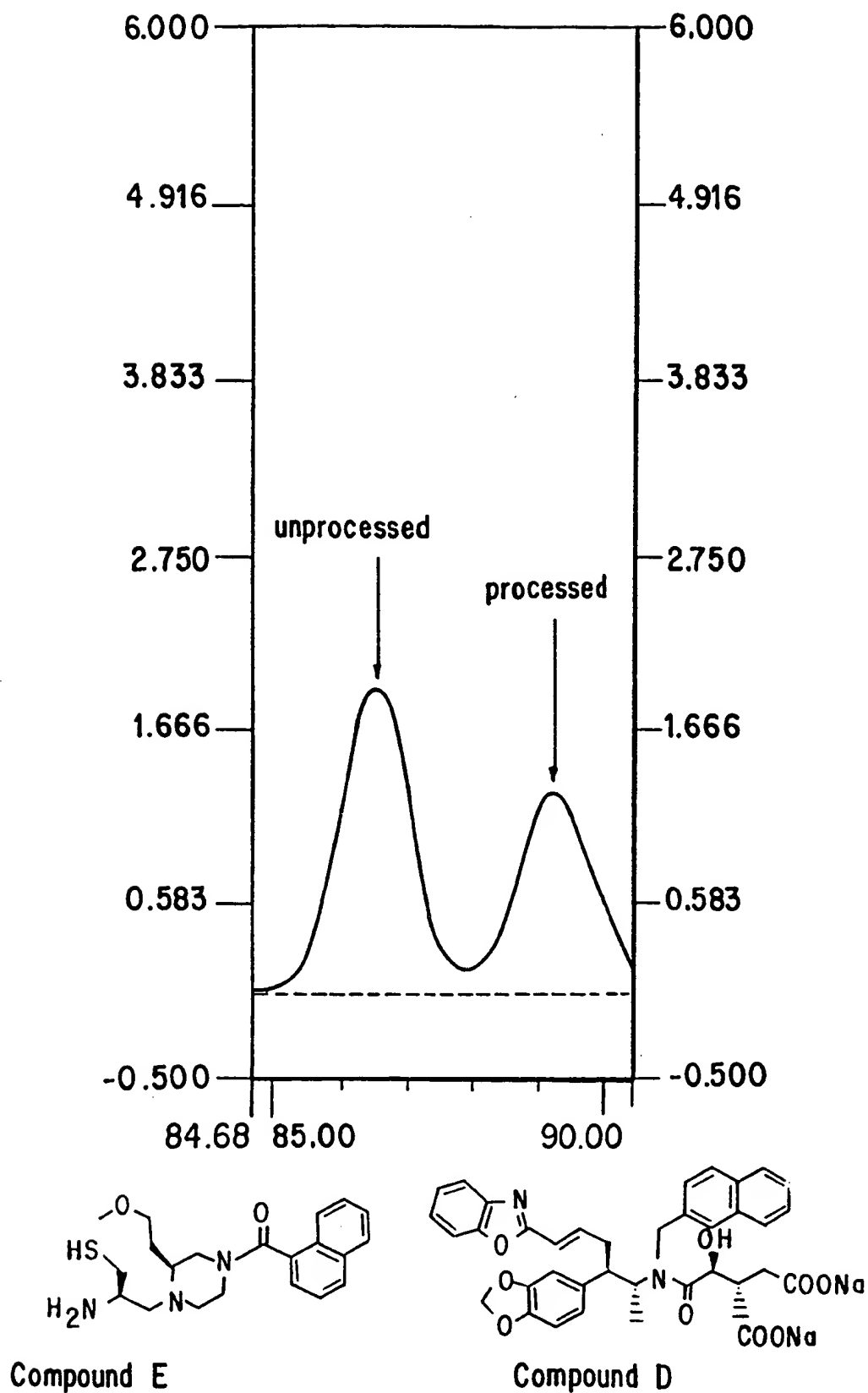


FIG. 1C

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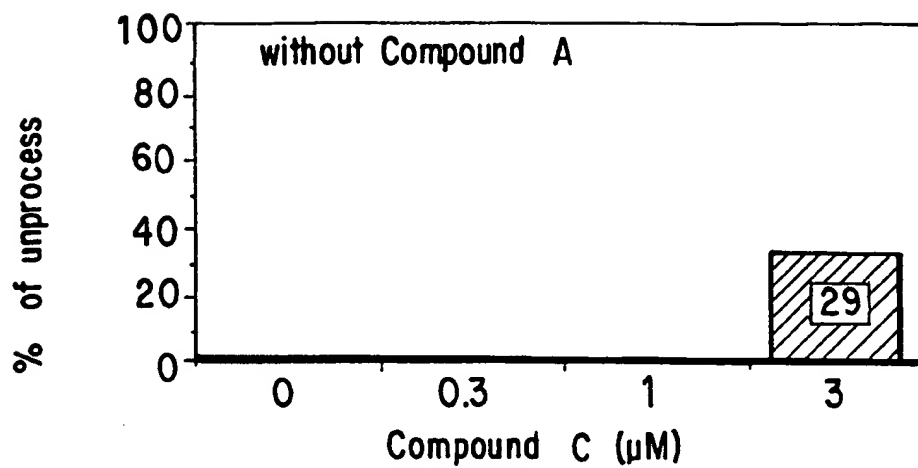


FIG. 2A

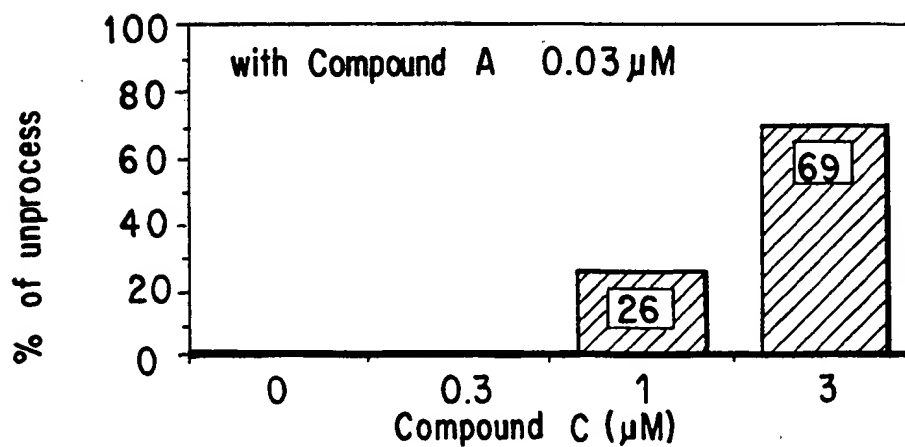


FIG. 2B

INTERNATIONAL SEARCH REPORT

 International application No.
 PCT/JS96/11022
A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A01N 37/18, 43/40; A61K 31/445, 38/00

US CL : 514/18, 357, 399, 562, 602, 630

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/18, 357, 399, 562, 602, 630

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.†
Y	US 5,340,828 A (GRAHAM ET AL.) 23 August 1994 (23.08.94), see entire document, especially columns 3-4.	1-6, 8-10, 12-19
Y	US 5,352,705 A (DEANA, DECEASE ET AL.) 04 October 1994 (04.10.94), see entire document, especially columns 3-4.	1-6, 8-10, 12-19
Y	US 5,362,906 A (ANTHONY ET AL.) 08 November 1994 (08.11.94), see entire document, especially columns 2-4.	1-6, 8-10, 12-19
Y	US 5,350,867 A (SINGH) 27 September 1994 (27.09.94), see entire document, especially columns 2-4.	1-6, 8-10, 12-19

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

03 SEPTEMBER 1996

Date of mailing of the international search report

04 OCT 1996

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
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Authorized officer

BENNETT CELSA

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/11022

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	WO 96/05168 A1 (BANYU PHARMACEUTICAL CO., LTD.) 22 February 1996 (22.02.96), see entire document.	1-19
Y	WO 95/00497 A1 (MERCK & CO., INC.) 05 January 1995 (05.01.95), see entire document.	1-19